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CLINICAL AND HEMATOLOGICAL ASPECTS OF ACUTE ERYTHROMYELOSIS

Studies of Three Patients

Sergio I. Magalini, M.D.,* and Lars Åhström, M.D.
Boston, Mass.

DI GUGLIELMO described the first case of erythroleukemia in 1917[1] and of pure acute erythromyelosis in 1923.[2] These diseases have in common a fundamental alteration of the erythroid series consisting of: (1) *hyperplasia;* (2) *anaplasia* (arrested maturation at primordial and immature stages); (3) *dysplasia* (alteration of the process of maturation resulting in nuclear and cytoplasmatic abnormalities); and (4) *metaplasia* (the presence and proliferation of erythroid cells at the sites of extramedullary hematopoiesis, as in the liver, spleen, kidney, testis, ovary, pancreas, etc.).

Several cases of DiGuglielmo's disease have been reported in adults and in children.[3-20] In the latter group, however, the differential diagnosis is at times more difficult. In childhood, because of a more labile hematopoietic system, diseases such as hemoglobinopathies, congenital hemolytic anemias, von Jaksch-Hayem-Luzet's anemia, may show an erythremic or erythroleukemic pattern as well.

At the Sixth International Congress of Hematology in 1956, DiGuglielmo reviewed the differential diagnosis of the erythremic diseases.[21] In their classification, many controversial aspects have now been clarified by the concept of myeloproliferative disorders.[22-24] This concept emphasizes the theoretical possibility of multiple involvement of all the bone marrow lines in production (erythro-myelo-megakaryocytic) simultaneously or successively in the majority of hematologic diseases. Thus, schematically, three types of disorders can be distinguished—the pure forms, the mixed forms, and the transient forms. On the basis of these classifications, the following types of erythremic diseases are recognizable (Table I).

The concept of myeloproliferative disorders was helpful in the explanation and assessment of some complex diagnostic problems among the 754

From The Children's Cancer Research Foundation and the Department of Medicine (Tumor Therapy), The Children's Medical Center, Boston, Mass.

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*Present address: Department of Internal Medicine, University of Rome, Rome, Italy.

TABLE I. POLYPHASIC MYELOPROLIFERATIVE DISEASES*

Pure erythromyelosis	→ Pure forms (permanent)	
	→ Polyphasic forms	→ Pure erythromyelosis ⟶ erythroleukemia
		→ Pure erythromyelosis ⟶ erythroleukemia ⟶ pure leukemia
		→ Pure erythromyelosis ⟶ erythroleukemia ⟶ pure leukemia ⟶ reticulosis
Erythroleukemia	→ Pure forms (permanent)	
	→ Polyphasic forms	→ Erythroleukemia ⟶ leukemia
		→ Erythroleukemia ⟶ erythromyelosis
		→ Erythroleukemia ⟶ leukemia ⟶ myelofibrosis

*Katsunuma (cited by DiGuglielmo[24]).

cases of acute leukemia in childhood (birth to 16 years) followed in the Tumor Therapy Clinic of The Children's Cancer Research Foundation in Boston (1947 to 1957). Only two instances of pure acute erythromyelosis and one of acute erythroleukemia, however, were found in this large group. Complete clinical and hematological details, together with the pathological findings in these three patients, will be presented and discussed in an attempt to contribute to a better understanding of some of the pathogenic mechanisms of these disorders.

CASE 1

J. P. was a 16-year-old white girl of Italian extraction. The family history was noncontributory. Past history revealed normal birth and development with regular immunizations and no illnesses other than repeated tonsillitis. In August, 1956, she had her first menses, which was neither profuse nor prolonged.

In 1954, following a dental extraction, the patient had alveolar oozing for approximately one month. No bleeding manifestations had been experienced before this episode, and none occurred subsequently until October, 1956, when one of the left lower molars was extracted and she again had an oozing of blood for a few days, with a probable infection at the site of extraction. Following this episode in October, she became increasingly more tired, developed shortness of breath on exertion, and appeared very pale. In the middle of December, 1956, the girl was admitted to an outside hospital where she was found to have a hemoglobin level of 3.9 Gm., red blood cells 960,000, and white blood cells 5,250. The differential was reported as follows: 38 per cent polymorphonuclear leukocytes, 36 per cent lymphocytes, 26 per cent "blast" forms, and numerous erythroblasts. The bone marrow biopsy was reported as consistent with acute leukemia. She received prednisone and three blood transfusions and was then transferred to the Tumor Therapy Clinic of The Children's Cancer Research Foundation on Jan. 4, 1957.

Physical examination showed a pale, slightly jaundiced, well-nourished, and well-developed 16-year-old girl, weighing 46 kilograms. There were no petechiae or ecchymoses. The liver was palpable 3 cm. below the right costal margin, the spleen 5 cm. below the left costal margin. There was generalized moderate shotty lymphadenopathy. The rest of the examination was noncontributory.

The clinical condition was unusually good and the girl was followed on an outpatient basis, with frequent visits. She remained clinically well until the end of March, 1957, when her condition began to deteriorate. She developed a sore throat (*Staphylococcus aureus*) and epistaxis. On April 10 she was admitted to the hospital.

On examination, the weight was 42 kilograms, the temperature 39° C. The skin was hirsute, with facial acne. No ecchymoses or petechiae were seen. There were monilia-like patches over the hypertrophic gums, tongue, and buccal mucosa. Bleeding points were seen along the soft and hard palate, and the tonsils were covered with white confluent patches. The upper gum, along the hard palate, was heavily infiltrated with a necrotic, soft, purulent mass measuring 1.5 by 3 cm. Submaxillary and cervical nodes were massively enlarged. The liver was now palpable 5 cm. below the right costal margin, and the spleen at the left iliac crest. The rest of the examination was noncontributory.

The mass in the oral cavity grew rapidly to involve the buccal mucosa, causing her much pain and preventing her from eating. She had a spiking temperature, up to 41° C. There were no hemorrhagic symptoms. She died

quietly on April 21, 1957, three and one-half months after her first visit to the Tumor Therapy Clinic, and about six months after the onset of the disease.

HEMATOLOGIC EVALUATION (CASE 1)

Peripheral Blood (Table II).—The erythroid series showed hypochromic anemia (mean corpuscular

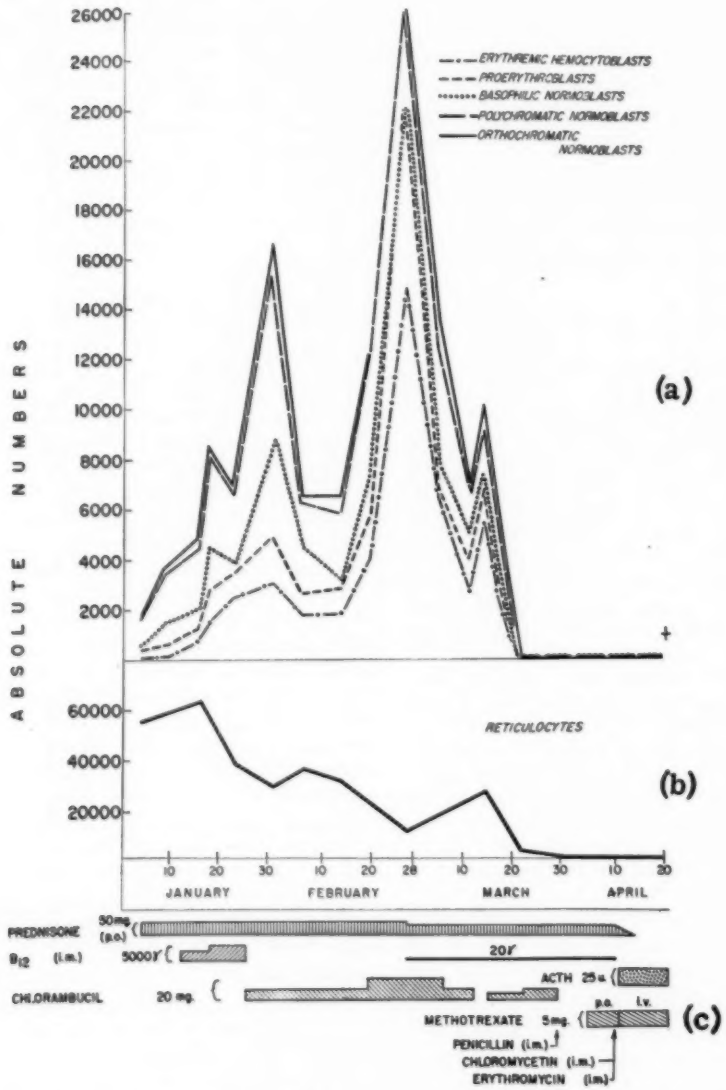

Fig. 1.—Case 1. *a*, Absolute numbers of nucleated red cells. *b*, Reticulocytes in the peripheral blood. *c*, Treatment.

hemaglobin 25.9γγ), with anisopoikilocytosis. Spherocytes, numerous schizocytes, and polychromatic cells were present, some of which were definitely basophilic while others showed a heavy basophilic stippling. Rouleaux formation was also occasionally observed. At first the reticulocytes were 1.9 per cent, but they decreased progressively to complete disappearance during the course of the disease. Frequent blood transfusions kept the hemoglobin range between 6 and 10 Gm.

cleocytoplasmatic asynchronism of maturation. The percentage of the more immature forms increased during the course of the disease (Fig. 2). Hiatus erythremicus* was noted occasionally. The absolute number went through three main periodic rises with intervals of temporary decreases, each rise being greater than the one preceding. Following the last, a steady decrease to complete disappearance of nucleated red cells was observed. In relation to the total nucleated cells

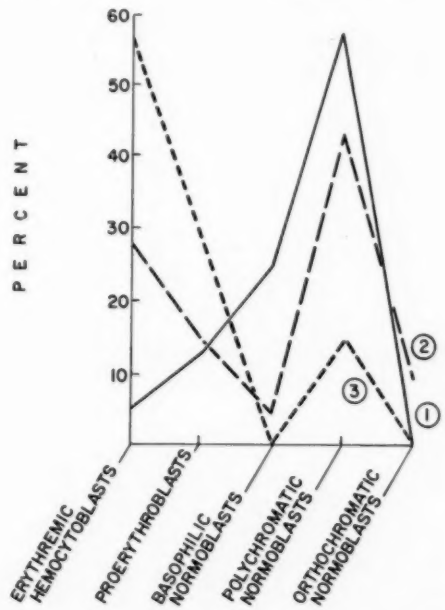

Fig. 2.—Case 1. Samples of the percentual distribution of nucleated red cells in the peripheral blood during the course of the disease.
1, January 9. *2*, February 14. *3*, February 27.

The peripheral blood was characterized by: (a) nucleated red cells, and (b) cells difficult to classify ("blasts" in Table II). All types of nucleated red cells were represented (Fig. 1). Many of them showed severe alterations such as karyolysis, severe nu-

they ranged from 49.2 per cent in the beginning to none at the end.

The other cells present (Figs. 3, 4) were usually round in shape, often

*"Hiatus erythremicus"—many young forms and many mature forms present, but the intermediate forms are missing (Fig. 14). (Compare with hiatus leukemicus of Naegeli.)

TABLE II. CASE 1

DATE	TOTAL NUCLEATED CELLS/ MM.³	"BLASTS"*	NUCLEATED RED CELLS/ MM.³ TOTAL*	WHITE CELLS TOTAL*	MYELO-BLASTS	PROMYELO-CYTES	MYELO-CYTES	METAMYELO-CYTES	MATURE GRANULO-CYTES	LYMPHO-CYTES	MONO-CYTES
Jan. 4	3,100	898 28.9%	1,404 45.3%	798 25.7%	-	-	18 2.2%	-	509 63.7%	254 31.8%	17 2.2%
Jan. 9	7,100	1,369 19.2%	3,500 49.2%	2,231 31.4%	-	17 0.8%	18 0.8%	-	1,530 68.5%	612 27.4%	54 2.4%
Jan. 16	13,700	3,960 28.9%	4,690 34.1%	5,050 36.8%	-	-	100 1.9%	-	3,960 78.4%	900 17.1%	90 1.7%
Jan. 18	21,700	6,600 30.4%	8,220 37.8%	6,880 31.7%	-	-	130 1.9%	-	5,650 82.1%	1,100 15.9%	-
Jan. 23	17,700	5,510 31.3%	6,800 38.2%	5,390 30.5%	110 2.0%	110 2.0%	-	-	4,150 76.9%	870 16.1%	150 2.8%
Jan. 31	47,000	21,060 44.8%	16,500 35.0%	9,440 20.0%	-	-	-	-	8,240 87.2%	600 6.3%	600 6.3%
Feb. 6	28,000	15,090 53.8%	6,450 23.0%	6,460 23.0%	-	-	-	-	6,250 96.7%	210 3.2%	-
Feb. 14	37,200	26,721 71.8%	6,500 17.3%	3,979 10.7%	-	-	-	-	3,670 92.2%	309 7.8%	-
Feb. 20	96,000	75,200 78.3%	12,450 13.0%	8,350 8.7%	-	-	-	-	8,350 100%	-	-
Feb. 27	89,000	51,192 57.5%	25,800 29.0%	12,008 13.4%	-	-	629 5.5%	-	10,750 89.2%	629 5.3%	-
March 6	56,000	34,900 62.3%	13,500 24.2%	7,600 13.5%	-	-	425 5.5%	-	7,175 94.4%	-	-
March 12	26,900	16,900 62.8%	6,950 25.9%	3,050 11.3%	-	-	-	-	2,800 91.8%	250 8.2%	-

March 15	71,000	55,600 78.3%	9,800 13.8%	5,600 7.8%	-	-	-	-	4,300 76.7%	1,300 23.2%	-
March 18	86,000	71,280 82.8%	4,860 5.7%	9,860 11.4%	-	-	-	-	5,680 57.6%	4,180 42.4%	-
March 26	285,000	270,750 95.0%	-	14,250 5.0%	-	-	-	-	8,500 60.7%	5,700 39.3%	-
March 29	294,200	279,490 95.0%	-	14,710 5.0%	-	-	-	-	10,885 74.1%	3,825 26.0%	-
April 1	191,000	183,950 96.3%	-	7,050 3.7%	-	-	-	-	5,140 73.1%	1,910 26.9%	-
April 3	271,000	267,340 98.6%	-	3,660 1.4%	-	-	-	-	3,660 100%	-	-
April 5	322,000	318,780 99.0%	-	3,220 1.0%	-	-	-	-	3,220 100%	-	-
April 8	244,000	237,400 97.4%	-	6,600 2.6%	-	-	-	-	4,880 73.9%	1,720 26.9%	-
April 10	232,000	229,680 99.0%	-	2,320 1.0%	-	-	-	-	1,620 69.9%	700 30.1%	-
April 17	325,000	320,775 98.4%	-	4,225 1.6%	-	-	-	-	4,225 100%	-	-

*Absolute number and percentage of total nucleated cells.

showing small protrusions of the cytoplasm. They presented a marked basophilic cytoplasm, peroxidase stain negative. The nucleus was large, covering three fourths of the cell and presenting a uniformly delicate structure. In some of the elements, however, the nucleus had a "combed-out" appearance. One to four colorless nucleoli were present, not clearly defined.

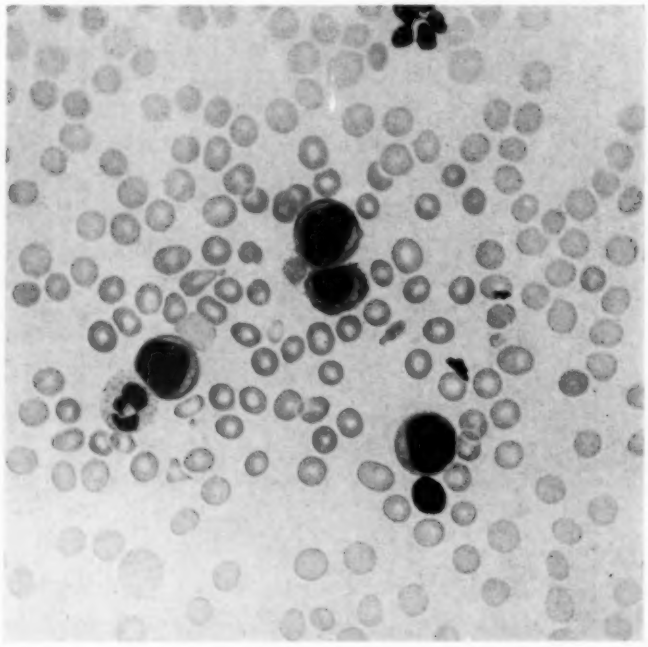

Fig. 3.—Case 1. Photomicrograph of the peripheral blood showing: (a) Presence of nucleated red cells. (b) Alterations of the erythrocytes. (c) Mature multilobulated granulocytes. (d) "Blasts" (see text). (×700.)

Among these cells many showed a definite halo on the side of the nucleus (initial hemoglobinization?) and they were included in the nucleated red-cell group as hemocytoblasts with erythroid characteristics. The remaining cells were considered in a block ("blasts") as precursor (hemohistioblasts, hemocytoblasts)[5, 7, 25, 26] and abnormal prehemoglobinized erythroid cells (paraerythroblasts of DiGuglielmo).[3, 7, 10, 13] The exact classification of these cells still remains an open question.

The number of these "blasts" steadily increased during the course of the disease (Fig. 5). This increase may be represented by a straight line when the logarithmic value of the cells is plotted against time. The slope of the best interpolating line calculated by the method of the least squares was 0.0222 ± 0.0016. The trend among the various values was found to be highly significant. Coincidental to the administration of a high amount of chlorambucil (0.420 mg. per kilogram per day), temporary interruption of

the rise in number of these cells was observed.

The myeloid series was mainly represented by extremely mature granulocytes. Their number ranged between 800 and 14,700 per cubic millimeter.

Lymphocytes, initially within normal range, were characteristically depressed by the treatment with chlorambucil.[27] Monocytes were occasionally present. Platelets averaged around 50,000 per cubic millimeter. Two sud-

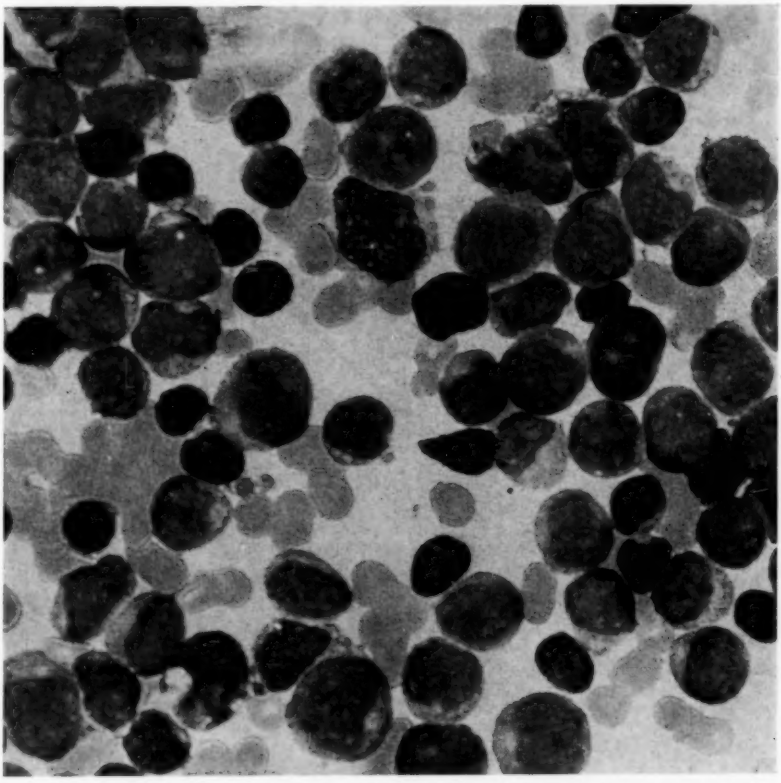

Fig. 4.—Case 1. Photomicrograph of the peripheral blood (sic) showing the marked hypercellularity and the anaplastic types of cells (final stage of the disease).

These were characterized by multilobulated nuclei, most of them presenting small pediculated buds (Karyoschizes), and lack of the specific neutrophil granulation, the eosinophils and basophils having normal granulation. Correction of this lack of neutrophilic granulation was noted in coincidence with vitamin B_{12} therapy.

den elevations in the count seem to have been related to discontinuation of therapy (chlorambucil).[27]

Tests.—

The blood group O, Rh positive.

The total serum bilirubin on January 4 was 1.5 mg. per cent, free, 0.5 mg. per cent.

On March 29 it was 1.3 mg. per cent, free, 0.2 mg. per cent.

*Serum Iron** determinations were as follows:

January 4	250 γ per cent
January 31	280 γ per cent
February 27	157 γ per cent
March 6	140 γ per cent
March 9	130 γ per cent

Electrophoretic migration of protein, lipoprotein, and glycoprotein was within normal limits.

Electrophoretic migration of hemoglobin was normal.

Repeated skeleton surveys and chest x-rays were negative.

Bone Marrow.—

Five bone marrow samples were obtained during the course of the disease by trephine biopsy, aspiration, and curettage. The examination was carried out on the smears, the sections of the clotted sample, and the biopsy,

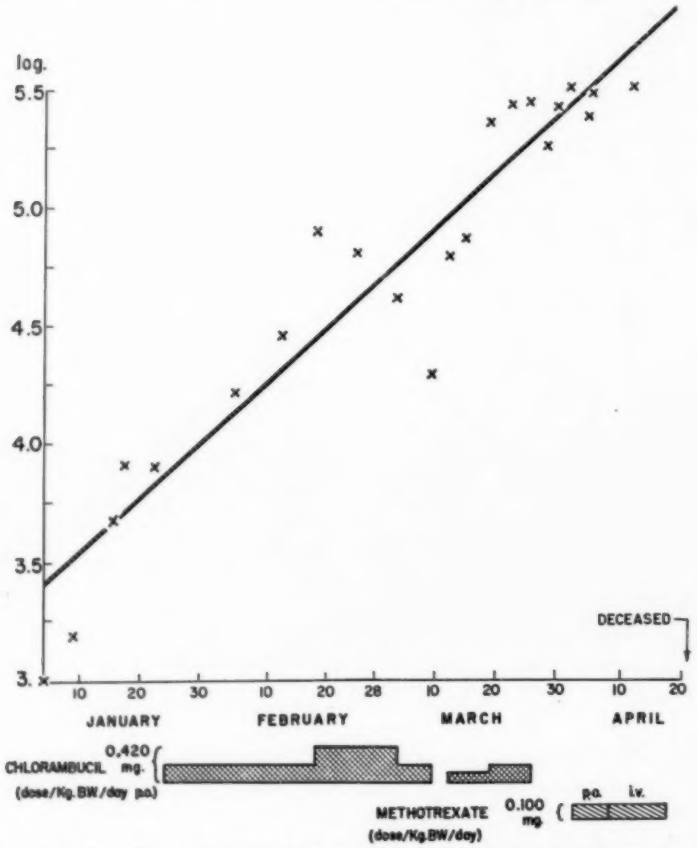

Fig. 5.—Rate of the increase of the "blasts" plus erythroid hemocytoblasts in the peripheral blood. This rate is represented by a straight line in a semilogarithmic system. Ordinate: logarithms of the number of "blasts." Abscissa: time in days.

The Coombs test, direct and indirect, was repeatedly negative.

*Normal value of serum iron 90 to 150 gamma per cent.

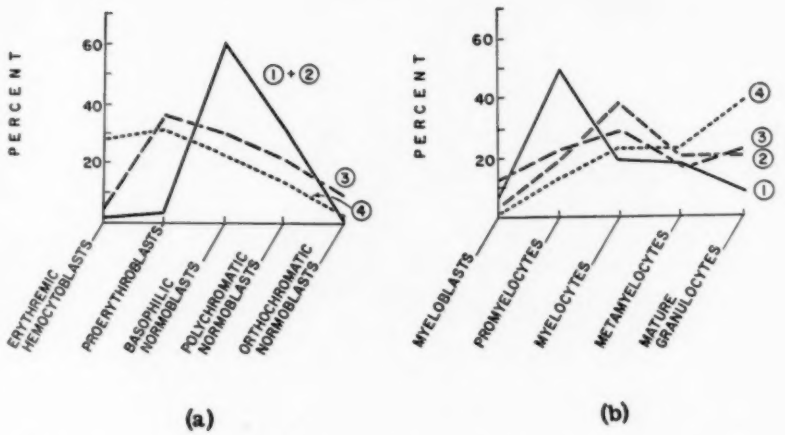

Fig. 6.—Case 1. *a*, Maturation curves of the erythroid series in the bone marrow. *b*, Maturation curves of the myeloid series.
1, January 10. *2*, January 21. *3*, February 13. *4*, March 15.

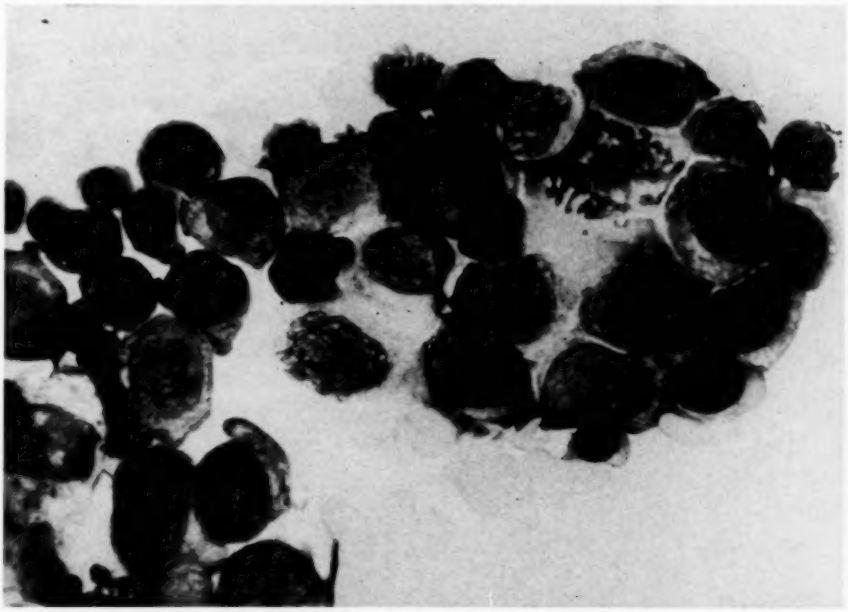

Fig. 7.—Photomicrograph of the bone marrow aspirate showing the typical arrangement of the erythroid cells with the immature elements in the center (one in mitosis) and the maturing one in the periphery. (×850.)

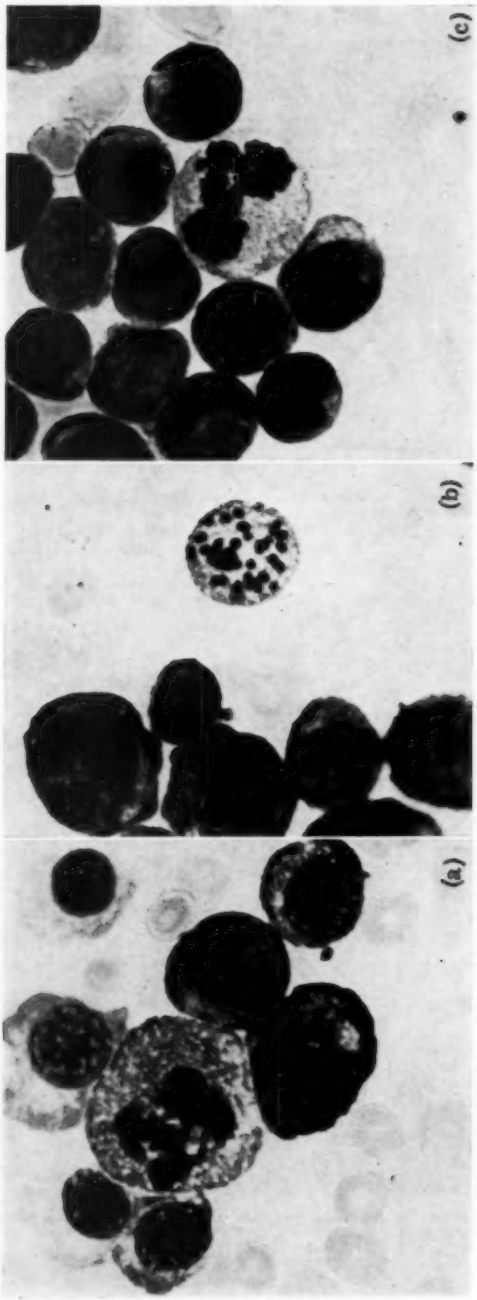

Fig. 8, a-c. *(For legend see opposite page.)*

Fig. 8.—Photomicrographs of some pathologic aspects of the mitosis observed in the erythroid cells in acute erythemia. (×1,100; reduced ⅓.) *a*, Abnormal anaphase. *b*, Metaphase (scattering chromosomes). *c*, (?) Tripolar division or division of lobated nucleus. *d*, Tripolar division. *e*, (?) Abnormal mitosis.

and the maturation curves were done on smears from the bone marrow aspirate. Two hundred to four hundred cells of the erythroid and myeloid series were counted by each author. From the average results, maturation curves[28] were plotted, and the erythroid:myeloid ratios calculated.

All the bone marrow specimens were markedly hypercellular. Their most striking feature was the erythroid hyperplasia.

Erythroid:myeloid ratio* was as follows:

January 10	18.0:1
January 21	5.2:1
February 14	3.0:1
March 15	12.5:1
April 11	Bone marrow completely replaced by "blasts"

The erythroid elements, their type and percentage, are illustrated by the maturation curves (Fig. 6, *a*) which, in the beginning, show an arrest of maturation at the level of the basophilic normoblast. A progressive shift to the left was observed as the course of the disease advanced. The successive curves showed an increase of hemocytoblasts with erythroid characteristics and proerythroblasts and a steady decrease of polychromatic and orthochromatic normoblasts. The elements described as "blasts" progressively increased from 1.8 per cent of the total nucleated cells in the first bone marrow specimen to 99 per cent of the total nucleated cells in the last. The erythroid elements, some of them "megaloblastiform," showed pathological changes such as nucleocytoplasmatic asynchronism of maturation, karyolysis, and multinucleated cells. Most of the cells were arranged in a pattern similar to islands of erythroid tissue with the more immature cells in the center and the mature on the periphery[3, 29] (Fig. 7). There were always large numbers of mitotic figures in these marrow samples averaging about 4 in 100 cells; most of them appeared to be within normal limits; some, however, appeared abnormal (Fig. 8). Their interpretation was extremely difficult since no particular technique for studying mitosis was used in the bone marrow samples.

The myeloid series in type and percentage is graphically illustrated by the maturation curves (Fig. 6, *b*). An arrest of maturation at the level of the promyelocytes was noted in the first bone marrow specimen but this was gradually brought to normal during the course. In the first two samples, a lack of neutrophilic granulation was also noted, which was later corrected.

The megakaryocytic series was always very poorly represented in number and functional activity. Moderate increase in the number of megakaryocytes was noted during the chlorambucil treatment.

The clinical and hematological findings point to a diagnosis of acute erythromyelosis, evolving progressively toward more and more immature anaplastic stages (histiomyelosis).

Pathological Diagnoses.—

Specific infiltration of bone marrow, spleen, lymph nodes, liver (minimal), heart, skin, muscles, esophagus, stomach, vagina, adrenals, kidneys, and trachea by cells of the same type as seen in the bone marrow biopsies during life.

Focal necrosis of the spleen.

Infarcts of the spleen with superimposed monilial growth.

*Normal E:M ratio, 1:2 to 1:4.

Ulcerations of esophagus and stomach with secondary bacterial and monilial infection.

Venous thrombosis of stomach and kidneys.

Hepatomegaly (2,100 grams compared with normal 1,400).

Splenomegaly (580 grams compared with normal 135).

Lymphadenopathy.

Hypertrophy of the heart with fatty infiltration.

Thrombocytopenia: megakaryocytosis of the spleen; hemorrhages of heart, lungs (severe), esophagus, gastrointestinal tract, kidneys, muscles, trachea, and spinal cord.

Therapeutic effect: depletion of the infiltrates; lymphoid depletion; fibrosis of the spleen; fibrosis of the lymph nodes; fibrosis of the pancreas, slight, focal; hemosiderosis of spleen and liver; habitus suggestive of Cushing's syndrome; hypertrophy of adrenals.

Aspiration, terminal, with necrotizing bronchopneumonia, focal.

Hirsutism.

Fat depletion of the adrenals.

Fatty changes of the liver.

Chronic pleuritis.

Bacteriology:

Heart:	No growth
Lungs:	*B. coli*
	Alcaligenes fecalis
Gut:	*Candida albicans*
Spleen:	*Candida albicans*

CASE 2

A. G. was a white boy, aged 4 years and 9 months. The father was Scandinavian, the mother English. There were three siblings, all well. There was no history of neoplastic disease. The child's birth and physical development were normal. At 3 months of age, a congenital hydrocele was repaired and at age 2 years a tonsillectomy was performed. Since that time the child had remained well until the present illness. There were no immunizations. It was noted that he had always had a rather enlarged abdomen.

Early in February, 1952, at 4 years and 7 months, the boy presented edema of the legs, which was followed a few days later by facial edema. There was no preceding sore throat or fever. On Feb. 13, 1952, he was brought to a local hospital where physical examination revealed a shotty midcervical adenopathy; the liver was palpable 6 cm. below the right costal margin; the spleen extended 10 cm. below the costal margin; there were edema of the legs and a fine petechial rash over the buttocks, elbows, and forehead. The hemoglobin was 9.9 Gm., erythrocyte count 4.7 million, leukocyte count 10,800, platelets 75,000. The peripheral smear contained "numerous immature red cells" and the bone marrow (Feb. 22, 1952) "showed extensive erythroid hyperplasia." The Coombs test, indirect and direct, was negative. Total serum bilirubin was 0.8 mg. per cent. Urinalysis was normal. Nonprotein nitrogen was 43 mg. per cent. X-rays of the chest and skull and an intravenous pyelogram were negative.

The boy spent 24 days in the hospital and the course was uneventful with the exception of lobar pneumonia that responded well to antibiotics. During hospitalization, the child received one blood transfusion when the hemoglobin dropped to 8 Gm. A few days after discharge he presented new symptoms and a hemorrhagic type of measles was diagnosed by the local physician. He recovered from this episode spontaneously in about one week and was then sent to the Tumor Therapy Clinic of The Children's Cancer Research Foundation on April 5, 1952.

Physical examination showed a pale, chronically ill boy with petechiae scattered over his entire body. His weight was 18 kilograms. There were numerous small, hard, shotty lymph

TABLE III

DATE	TOTAL NUCLEATED CELLS/MM.³	NUCLEATED RED CELLS						RETICULOCYTES (%)	RBC (×10⁶)	HEMOGLOBIN (GM.)
		TOTAL*	HB†	PE†	BN†	PN†	ON†			
April 5	5,600	554 9.9%	–	50 9.0%	101 18.0%	356 64.0%	50 9.0%	10.0	3.29	6.8
April 16	2,750	–	–	–	–	–	–	13.0	4.11	8.2
April 23	4,750	137 2.9%	–	–	–	137 100%	–	1.2	3.65	10.3
May 2	6,600	125 1.9%	–	–	–	125 100%	–	2.6	4.00	8.9
May 6	12,350	1,111 9.4%	–	111 10.0%	555 50.0%	111 10.0%	333 30.0%	3.0	3.50	7.9

*Absolute number and percentage of total nucleated cells.
†HB, hemocytoblast. PE, proerythroblast. BN, basophilic normoblast. PN, polychromatic normoblast. ON, orthochromatic normoblast.

nodes in the cervical, axillary, and inguinal regions. The liver was palpable 10 cm. below the right costal margin, the spleen 19 cm. below the left costal margin. The rest of the examination proved noncontributory.

A diagnosis of acute erythromyelosis was made on laboratory findings (see Hematologic Evaluation) (Table III).

The child was hospitalized. His clinical condition at first was fair and he spent most of the time up and about. There was no change in the size of the spleen, liver, or lymph nodes. After one month in the hospital he developed fever and further distention of the abdomen accompanied by pain, with no indication as to origin. Nose, throat, and blood cultures were negative. Death occurred during sleep, five days after this episode started, and three months after the onset of first symptoms.

HEMATOLOGIC EVALUATION (CASE 2)

Peripheral Blood (Table III).—

The erythroid series showed hypochromic anemia (mean corpuscular hemoglobin 20.6 $\gamma\gamma$) with anisopoikilocytosis, slight to moderate spherocytosis, with the presence of schizocytes and polychromasia. Following admission, the hemoglobin values were kept at a level between 9 and 11 Gm. by blood transfusions. A significant decrease in the number of reticulocytes was noted after the first transfusion. Since then they had remained within normal limits. Nucleated red cells were present throughout the course of the disease, their number ranging between 1 and 9 per cent of the total nucleated cell count. All elements were represented from the hemocytoblast with erythroid characteristics (cells described in Case 1) to the orthochromatic normoblast, the percentage of the more immature cells being increased in the terminal phase of the disease.

In the myeloid series, the corrected number of white cells remained within normal range (2,750 to 11,239 per cubic millimeter). A marked shift to the left was noted with no particular morphological alterations. The lymphocytes were low in number. The monocytes showed no significant change. Platelets were constantly low (3,000 to 38,000 per cubic millimeter).

A spontaneous diminution of all the nucleated cells from the initial value

CASE 2

	WHITE CELLS							
TOTAL*	MYELOBLASTS	PROMYELOBLASTS	MYELOCYTES	METAMYELOCYTES	POLYMORPHONUCLEAR LEUKOCYTES	LYMPHOCYTES	MONOCYTES	PLATELETS
5,046	150	50	400	550	2,750	700	400	19,000
90.1%	3.0%	1.0%	8.0%	11.0%	55.0%	14.0%	8.0%	
2,750	–	–	–	–	1,250	1,000	500	26,000
100%					45.0%	37.0%	18.0%	
4,613	350	150	150	260	2,453	600	650	38,000
97.1%	8.0%	2.0%	2.0%	8.0%	56.0%	13.0%	9.0%	
6,475	259	324	324	583	3,561	972	452	3,000
98.1%	4.0%	5.0%	5.0%	9.0%	55.0%	15.0%	7.0%	
11,239	450	225	674	337	7,305	1,348	900	–
90.6%	4.0%	2.0%	6.0%	3.0%	65.0%	12.0%	8.0%	

was noted, subsequently followed by a general rise.

Bone Marrow.—

Bone marrow samples were obtained as previously described in the data on Case 1, and maturation curves were done on the smears from the marrow aspirate. All the samples were markedly hypercellular, showing conspicuous erythroid hyperplasia.

Erythroid:myeloid ratios:

April 3	1:1
April 16	2:1
April 25	2:1

The erythroid elements, their type and percentage, are illustrated by the maturation curves (Fig. 9, *a*) which show a maturation arrest at the level of the basophilic normoblast in all samples and a marked increase of the

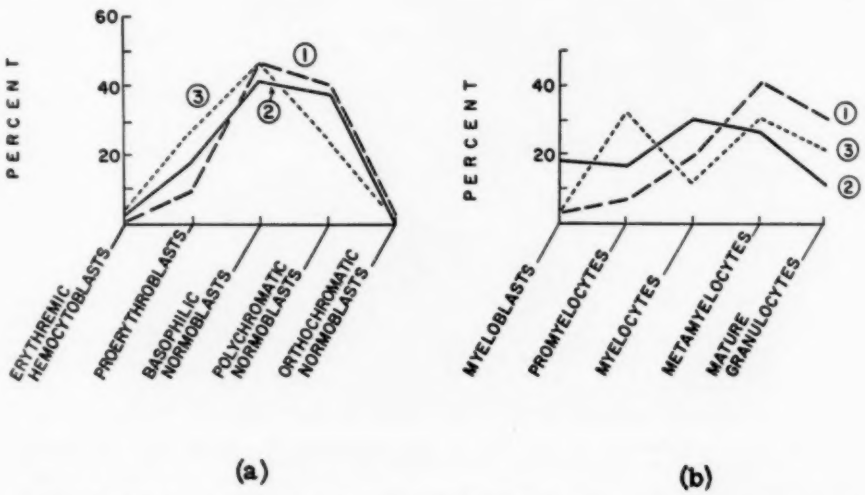

Fig. 9.—Case 2. *a*, Maturation curves of the erythroid series in the bone marrow. *b*, Maturation curves of the myeloid series.
1, April 3. *2*, April 16. *3*, April 25.

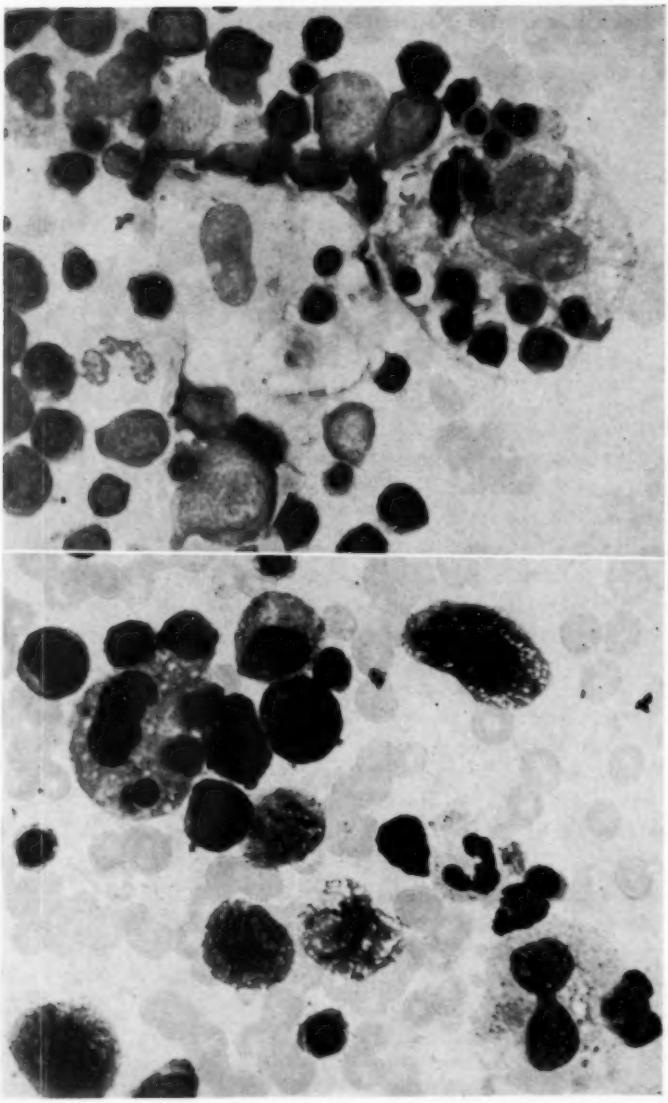

Fig. 10.—Photomicrographs of the bone marrow aspirate showing macrophages trapping numerous basophilic, polychromatic, and orthochromatic normoblasts. (×850.)

proerythroblasts and absence of orthochromatic normoblasts. In all three samples, about 20 per cent of all nucleated cells were represented by immature cells as the already described paraerythroblast. The pathological changes of the erythroid cells were identical with those in Case 1. An additional feature, however, was present in this patient's bone marrow—the presence of numerous macrophages, many of them containing nucleated red cells in all stages of maturation (Fig. 10). Mitotic figures were seen in an average of 4 in 100 cells, some of them suggesting abnormality (Fig. 8).

In the myeloid series (Fig. 9, *b*), the first curve shows a completely normal maturation. The second curve shows a shift to the left. The last obtained bone marrow specimen shows a diphasic type of curve, the result of an increase in promyelocytes and a decrease in myelocytes. No particular morphological changes were observed.

The megakaryocytes were extremely rare in all the bone marrow samples obtained.

Tests.—

The blood group was O, Rh positive.

The Coombs test, direct and indirect, was repeatedly negative.

Total serum bilirubin (April 7) 0.63 mg. per cent; free 0.25 mg. per cent.

Red-cell fragility was normal.

The tourniquet test was 3 plus, clotting time 2 minutes.

Repeated skeletal surveys and chest x-rays were negative.

Evaluation of the clinical and hematological findings points to a diagnosis of acute erythromyelosis evolving toward erythroleukemia. This diagnosis was confirmed at autopsy.

Pathological Diagnoses.—

Acute erythromyelosis, with infiltration of spleen, stomach, small intestine, appendix, colon, pancreas, liver, kidneys (Figs. 11, 12), bone marrow by cells of the same type as were seen in the bone marrow samples during life.

Lymphadenopathy, cervical, inguinal, axillary, portal, mesenteric, peripancreatic, periaortic, hilar, mediastinal.

Hemorrhage, petechial and ecchymotic, of skin, conjunctivae, kidneys, liver, lungs.

Leukocytosis due to immature erythroid cells.

Osteoporosis, moderate.

Edema of feet, thighs, perineum, mesentery, lungs.

Pleural effusion, bilateral (left 175 c.c., right 100 c.c.).

Atelectasis, bilateral, partial.

Fatty metamorphosis, liver.

Colloid depletion, thyroid.

Atrophy, thymus.

Hypotrophy, adrenals, with multiple cortical adenomas.

Scars, left cervical, and left knee.

Bacteriology:

Heart:	No growth
Lungs:	No growth
Pleural cavity:	No growth

CASE 3

D. B. was a white girl, aged 3 years and 2 months. The paternal grandmother had pharyngeal cancer. A cousin has diabetes. There were no siblings. Birth and development were normal. There were regular immunizations and the child remained in good health to the present illness.

At the end of July, 1956, the girl became anorexic and appeared tired. Soon thereafter she presented ecchymoses of the skin after very slight trauma. Weakness gradually increased

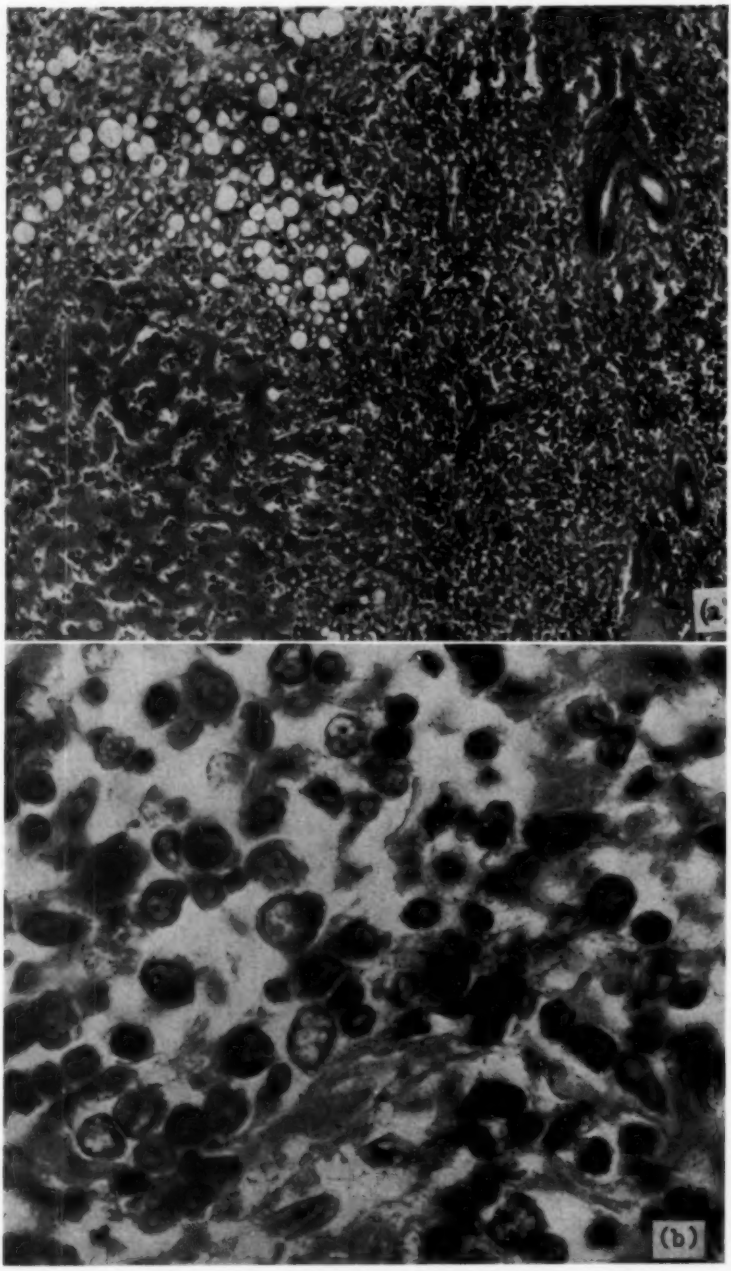

Fig. 11.—Photomicrographs of liver showing the heavy infiltration with immature erythroid elements and fatty metamorphosis. (*a*, ×200; reduced ⅓. *b*, ×1,250; reduced ⅓.)

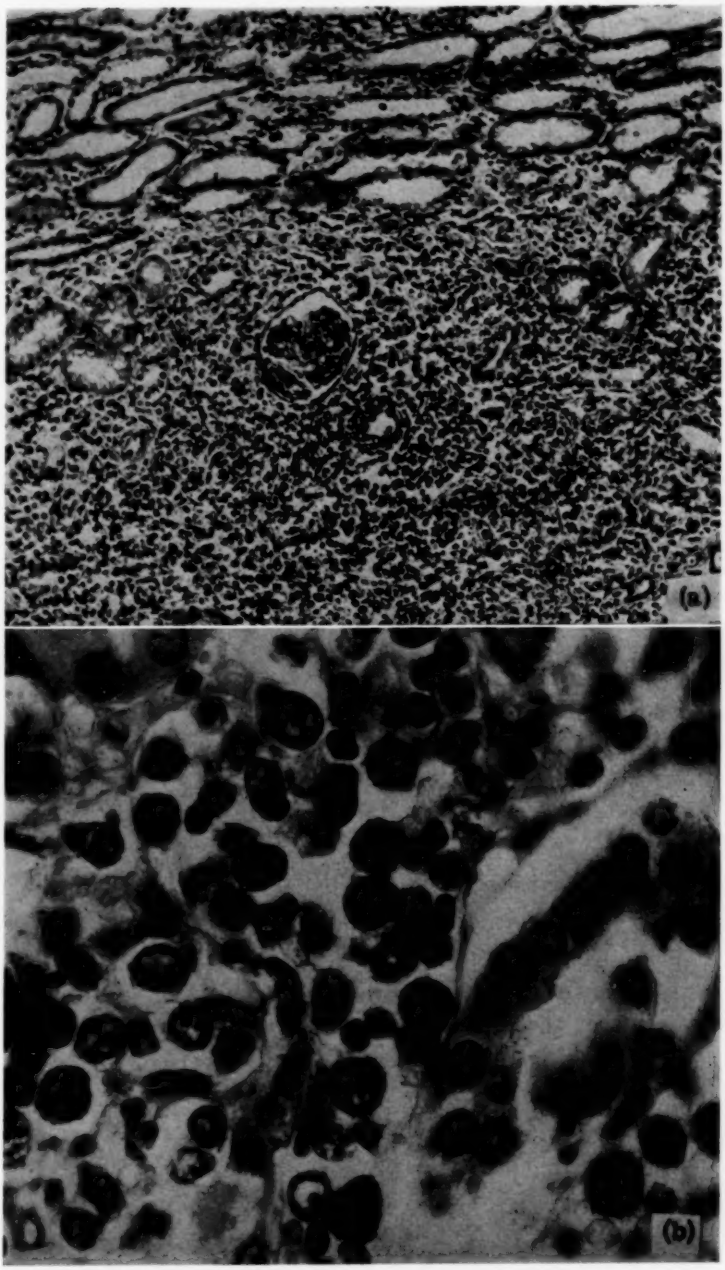

Fig. 12.—Photomicrographs of the kidney showing the heavy infiltration of the cortex by the immature erythroid cells. (*a*, ×200; reduced ⅙. *b*, ×1,250; reduced ⅙.)

TABLE IV. CASE 3

DATE	TOTAL NUCLEATED CELLS/ MM.³	"BLASTS"*	NUCLEATED RED CELLS/ MM.³ TOTAL*	WHITE CELLS TOTAL*	MYELO-BLASTS	PROMYELO-CYTES	MYELO-CYTES	METAMYELO-CYTES	MATURE GRANULO-CYTES	LYMPHO-CYTES	MONO-CYTES
Sept. 21	24,000	10,250 42.7%	8,250 34.2%	5,500 22.9%	789 14.3%	945 17.2%	1,100 20.0%	160 2.9%	2,020 36.7%	472 8.6%	14 0.3%
Sept. 27	25,000	13,340 53.4%	7,000 28.0%	4,660 18.6%	180 3.9%	180 3.9%	900 19.3%	180 3.9%	2,160 46.4%	1,060 22.7%	–
Oct. 3	72,000	38,700 53.8%	23,000 32.0%	10,300 14.2%	–	–	4,900 47.6%	–	5,400 52.4%	–	–
Oct. 11	72,000	48,400 67.2%	17,000 23.6%	6,600 9.2%	–	–	2,200 33.3%	500 7.6%	3,350 50.8%	550 8.3%	–
Oct. 18	15,900	7,490 47.1%	5,220 32.8%	3,190 20.1%	–	–	210 6.6%	300 9.4%	1,190 37.3%	1,280 40.1%	210 6.6%
Oct. 25	20,200	11,530 57.1%	5,250 26.0%	3,420 16.9%	–	300 8.8%	745 21.8%	–	1,045 30.6%	730 21.3%	600 17.6%
Oct. 28	37,000	17,200 46.5%	11,650 31.5%	8,150 22.0%	–	500 6.1%	750 9.2%	200 2.4%	2,000 24.5%	3,700 45.4%	1,000 12.2%
Nov. 8	89,000	52,700 59.2%	18,900 21.2%	17,400 19.6%	–	2,100 12.1%	2,800 16.1%	1,000 5.8%	6,700 38.6%	2,700 15.6%	2,100 12.1%
Nov. 15	40,000	22,050 55.1%	7,500 18.7%	10,450 26.1%	–	325 3.1%	975 9.3%	880 8.4%	4,050 38.8%	4,220 40.4%	–
Nov. 21	24,400	14,685 60.2%	4,570 18.7%	5,145 21.1%	–	198 3.8%	390 7.6%	170 3.4%	3,000 58.3%	1,190 23.1%	197 3.8%
Nov. 27	19,100	15,870 83.1%	1,350 7.0%	1,880 9.9%	–	178 9.5%	178 9.5%	106 5.6%	1,240 65.9%	178 9.5%	–
Dec. 4	15,100	11,690 77.4%	1,180 7.8%	2,230 14.8%	–	140 6.3%	570 25.6%	100 4.5%	600 27.0%	700 31.5%	120 5.4%
Dec. 17	18,100	14,360 79.3%	1,340 7.4%	2,400 13.3%	–	–	302 12.6%	50 2.0%	302 12.6%	1,676 69.8%	70 2.9%
Dec. 24	44,800	30,620 68.4%	4,600 10.3%	9,580 21.3%	–	810 8.5%	2,820 29.4%	410 4.3%	2,020 21.1%	2,420 25.3%	1,100 11.5%
Dec. 31	43,000	18,560 43.2%	5,950 13.8%	18,490 43.0%	1,480 8.0%	2,960 16.0%	7,050 38.1%	1,520 8.2%	3,300 17.8%	740 4.0%	1,440 7.8%

*Absolute number and percentage of total nucleated cells.

and in mid-September she had a severe epistaxis and was admitted to the Tumor Therapy Clinic of The Children's Cancer Research Foundation.

Physical examination showed a well-developed white girl who weighed 15 kilograms. She was pale, and there were multiple ecchymoses. The liver was palpable 4 cm. below the right costal margin, the spleen 6 cm. below the left costal margin. There was generalized shotty lymphadenopathy. The rest of the examination was noncontributory. The blood group was O, Rh negative. A diagnosis of acute erythroleukemia was made from the laboratory findings (see Hematologic Evaluation).

The child was started on folic acid antagonist and, because of a general clinical improvement, was discharged from the hospital one week after admission. Shortly after, because of severe epistaxic, fever, and hematemesis, she was readmitted to the hospital, following which her condition slowly deteriorated, with no significant change in the hematological status.

Severe hemorrhagic manifestations and infections dominated the clinical picture. Seven weeks before she died, she developed a *Staphylococcus aureus* septicemia. During the last three weeks she was semiconscious, refused to take anything by mouth, had a high spiking fever (40 to 41° C.), melena, hematemesis, hematuria, and was covered with petechiae and ecchymoses. She also presented a generalized moniliasis. The spleen and liver were enlarged to the iliac crests.

The child died quietly on Jan. 6, 1957, three and one half months after her first admission, and five and one half months after onset of symptoms.

HEMATOLOGIC EVALUATION (CASE 3)

Peripheral Blood (Table IV).—

Normochromic anemia (mean corpuscular hemoglobin 28.5γγ was present with a moderate anisopoikilocytosis, occasional spherocytes and schizocytes, and polychromia. The reticulocyte count remained within normal range. The hemoglobin varied between 4.6 and 11.2 Gm. during the course of the disease and was maintained by numerous blood transfusions.

The peripheral blood was characterized by the presence of: (a) nucleated red cells; (b) "blast" cells, resembling DiGuglielmo's "micro-erythroblasts"[4]; (c) immature myeloid cells (Fig. 13).

The nucleated red cells, presenting the same pathological findings as described in Case 1, were present all through the course, ranging in value from 7 per cent to 34.2 per cent of the total nucleated cells. Cells in all stages of maturation were represented; prevalence of the immature elements over the mature was constant and, occasionally, the hiatus erythremicus was observed (Fig. 14). The "micro-erythroblasts" were small, round, with an extremely thin rim of cytoplasm deeply basophilic, and a reticular dark nucleus occasionally presenting one to three colorless nucleoli. The number of these cells dominated the picture (Table IV) and their absolute number varied markedly. In the myeloid series the myelocytes were constantly present during the course of the disease, the promyelocytes occasionally, while the myeloblasts were found only at the first and last stages. No unusual morphological changes were noted.

Bone Marrow.—

Two samples were obtained and studied as previously described. Both samples were hypercellular and showed marked erythroid hyperplasia.

Erythroid: myeloid ratio was as follows:

September 19	1:2
October 23	3:1

* Absolute number and percentage of total nucleated cells.

The erythroid elements, their type and percentage, are illustrated by the maturation curves (Fig. 15, *a*). In both samples there was an arrest of maturation at the level of the basophilic normoblast. The orthochromatic normoblasts were practically absent. In addition, the same pathological changes noted in Cases 1 and 2 were apparent.

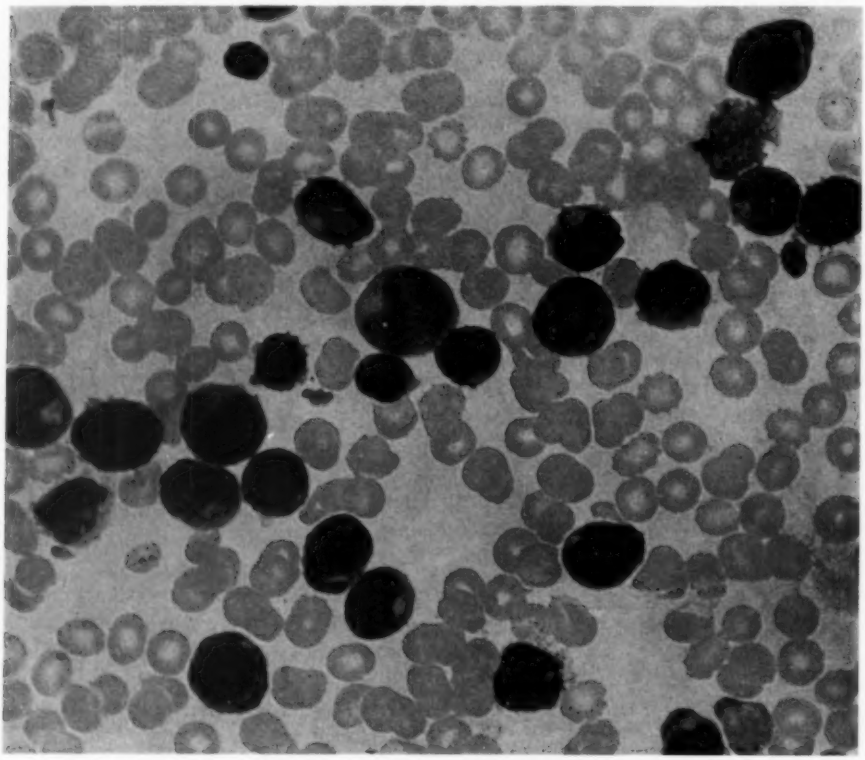

Fig. 13.—Case 3. Photomicrograph of the peripheral blood showing the presence of immature erythroid and myeloid elements. (×850.)

Numerous "paraerythroblasts" and "microerythroblasts" were present and some form of passage from these cells to the normal erythroid series was noted. Mitosis averaged around 1 in 100 cells.

The myeloid series (Fig. 15, *b*) showed marked increase of myeloblasts and promyelocytes and a marked decrease of the metamyelocytes and mature granulocytes. Myelocytes were practically absent. Megakaryocytes were extremely rare.

The clinical and hematological findings in this case point toward a diagnosis of acute erythroleukemia. The diagnosis was verified at autopsy.

Pathological Diagnoses.—

Leukemic infiltration of bone marrow, spleen, lymph nodes, kidneys, adrenals, urinary bladder, uterus, vagina, and Fallopian tubes, with the same type of cells as were seen in the bone marrow during life.

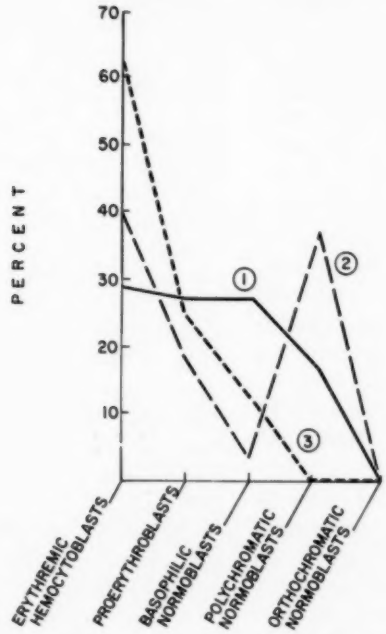

Fig. 14.—Case 3. Samples of the percentual distribution of nucleated red cells in the peripheral blood during the course of the disease.
1, September 21. *2*, November 8. *3*, December 17.

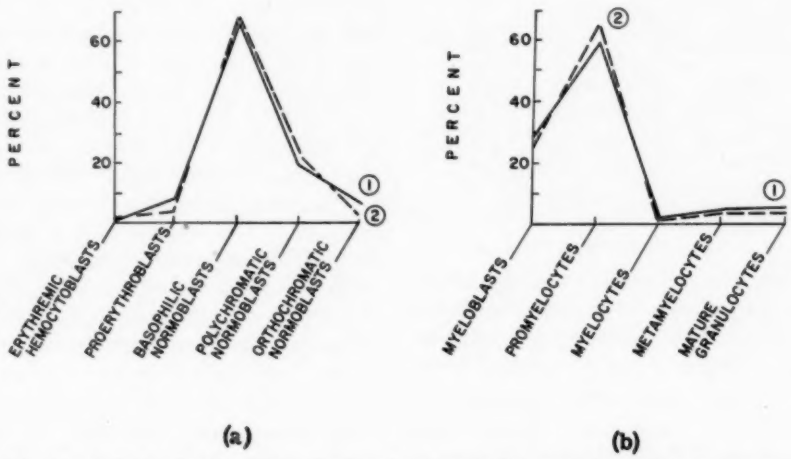

Fig. 15—Case 3. *a*, Maturation curves of the erythroid elements in the bone marrow. *b*, Maturation curves of the myeloid elements.
1, September 19. *2*, October 23.

Splenomegaly (115 grams compared with the normal 39).

Lymphadenopathy.

Thrombocytopenia with hemorrhages of heart, lungs, gastrointestinal tract, kidneys, urinary bladder, skin, lips, and gums.

Anemia with fibrosis of the heart.

Therapeutic effect (ACTH, mercaptopurine, transfusions): hyperplasia of the adrenals (with cytomegaly of the stratum fasciculatum); toxic gastritis; fibrosis of the spleen, slight; fibrosis of the bone marrow, slight, with focal necrosis of the costal metaphysis; hemosiderosis of spleen, liver, and lymph nodes.

Multiple bacterial and mycotic lesions: ulceration of the esophagus (? streptococcus); ulceration of the intestine (*B. coli*); ulceration of the vulva (agent undetermined); bronchopulmonary aspergillosis; moniliasis of liver and heart.

Fatty changes of the liver.

Meckel's diverticulum.

Bacteriology:

Heart: No growth
Lungs: No growth
Bowel: *E. coli*
Alpha hemolytic streptococcus

DISCUSSION

Various pathological changes in the erythroid series were encountered in a group of 754 children with miscellaneous types of acute leukemia. The particular combination, however, of the several pathological changes compatible with DiGuglielmo's disease was found to be extremely rare in this age group. Only two cases of acute erythromyelosis and one of erythroleukemia in children were diagnosed.

Hematologically and clinically, these cases were well characterized by hyperplasia, anaplasia, dysplasia, and metaplasia of the erythroid system, as well as by severe anemia, erythroblastosis (with steady increase in the circulation of progressively less mature erythroblasts), thrombocytopenia with hemorrhagic manifestations, hepatosplenomegaly, ulceronecrotic lesions of the oral cavity, intermittent fever, and, finally, the short and fatal course. The hematological and clinical manifestations of these diseases have been reported several times and extensively discussed. For this reason we shall limit our discussion to findings of particular interest presented by our three patients.

The severe, progressive anemia is particularly characteristic of these diseases. Numerous mechanisms have been implicated in its pathogenesis:

A. Decreased production of mature erythrocytes. Although the bone marrow is overcrowded with erythroid elements, the maturation of the red cells is usually arrested at a prehemoglobinized stage, as is well demonstrated by the reported maturation curves (Figs. 6, 9, 15), although, in the first stages of the disease, a certain percentage of erythroid cells still retain their ability to mature (hiatus erythremicus). In the natural progress of the disease, the reproduction of these cells stops, as is illustrated (Figs. 1 and 2) by the decrease and then the disappearance of the reticulocytes, the ortho- and polychromatic elements from the blood and the bone marrow.

B. The shorter life span of the erythrocytes. This, very likely, is due to intrinsic defects and/or abnormal formation indicated by the poor and irregular hemoglobinization and morphological changes.

C. Increased destruction. The hyperplasia of the reticuloendothelial system, increased erythrophagocytosis, and splenomegaly are constant findings in these diseases.

Usually, phagocytosis is directed against aged or damaged red cells, but in one of our patients (Case 2) the phagocytic activity was directed against all the erythroid elements. The bone marrow examinations revealed numerous macrophages which contained not only erythrocytes but all types of erythroid cells from the proerythroblast to the orthochromatic normoblast (Fig. 10). Together with the increased activity of the reticuloendothelial system, the cytological abnormalities and metabolic or immunological changes of the erythroid cell might be considered in an attempt to explain this finding.

In acute erythremic myelosis the presence of cells referred to as "megaloblastiform" has been reported.[3, 30] Similar cells were observed in one of our patients J. P. (Case 1). In this case, together with the presence of these megaloblastic cells, some macrosomia of the metamyelocytes in the bone marrow and a marked hypersegmentation of the nuclei of the mature granulocytes were observed. An interesting observation was the disappearance of these "megaloblastic" cells and the normalized maturation of the leukocytes in coincidence with the administration of high amounts of vitamin B_{12}. No changes, however, were noted in the progression of the anemia and the other pathological alterations of the erythroid cells. Thus, these megaloblastic changes might be interpreted as being due to a secondary deficiency of folic acid or vitamin B_{12} deriving from enormously increased cell reproduction. This interpretation coincides with the one given to explain the megaloblastic changes sometimes observed in the acute leukemias.[31]

Numerous findings indicate pathogenetic similarity between acute erythromyelosis, erythroleukemia, and malignant processes.[25, 32, 33] All three of our patients presented similar bone marrow changes and the maturation curves of the erythroid series showed a constant arrest of maturation. The persistent shift to the left as the disease progresses indicates that this inability to mature becomes more and more marked. Thus, the already increased production of immature elements encounters this block which moves steadily backward, resulting in an increase in the progressively less differentiated population of cells. This behavior will explain the various phases occurring during the evolution of this disease and may also be compared with that of some types of anaplastic malignancies where progressively undifferentiated cells may be observed.

Our three patients also showed extramedullary erythropoiesis. It may be seen that this finding of erythroid ectopic growth also appears to parallel the metastatic behavior of most malignancies, and should not be interpreted solely as a compensatory effort to control the anemia, since it was not limited to potential hematopoietic organs but was found, as well, in other organs such as the intestine, kidneys, pancreas, etc.

The progressive increase of the "erythroblasts" in the peripheral blood and their increasing immaturity are typical findings of the disease. The temporary spontaneous decrease

of the number of cells during the course has been noted in certain cases reported by other authors.

If the high myeloid component in Case 3 is excluded, the peripheral blood patterns of all three of our patients are found to have been qualitatively similar. Patient A. G. (Case 2) (Table III) showed only a limited number of circulating nucleated erythroid cells which, after a spontaneous reduction in number, increased once more. Patient D. B. (Case 3) (Table IV) showed a significantly higher number of circulating nucleated erythroid cells and the presence of cells defined as "microerythroblasts." It is possible that in this case the treatment may have affected the number of the circulating cells; however, they showed a general upward trend throughout the periodic variations. Case 1 demonstrated all the classic features of the erythremic picture, the progressive increase of erythroblasts and their increasing immaturity, their exhaustion and ultimate, complete substitution by anaplastic cells as the disease advanced in its course (Figs. 1, 2). The behavior of the immature cells ("blasts") was interesting. They increased steadily in a semilogarithmic fashion, a linear trend (Fig. 5) interpolated significantly among all the logarithmic values of the numbers of the cells. Considerable help in the interpretation of this finding is given by a study on the rate of cell division by Osgood.[34] He discovered that, while the reproduction of normal cells in growth plotted against time may be represented by a linear function in a log-log system, the growth in the early stages of division of organisms or tissue, and in malignancy, follows a straight line in a semilogarithmic system. The type of cells growing in this patient seems to be in line with the behavior of malignant growth.

Very little is known about the normal and pathologic production of cells in the hematopoietic organs and their release into the blood stream. Therefore, it is difficult to establish whether the logarithmic increase of cells in the circulation is merely the expression of growth of neoplastic cells in the bone marrow and other involved organs, or if it is evidence of invasion of the blood stream by dividing neoplastic cells. To explain the reproduction of these cells in the blood one must, however, postulate amitotic divisions, since search for the element in mitosis in the peripheral blood has been made without success, despite the fact that a particular technique was used (acetocarmine squash technique [alcohol-acetic acid 3:1]), to make more evident the mitotic divisions.

Acute erythromyelosis and acute erythroleukemia have a fatal course. No spontaneous or induced remissions have been reported, and therapeutic attempts to correct or modify the ultimate course have always been ineffective. Our three patients received treatment in accordance with the concept of "total care" described by Farber.[35, 36] In addition to the symptomatic treatment, whole blood and platelet transfusions, maintenance of electrolyte balance, antibiotics, etc., four different lines of therapeutic approach were followed:

1. Since, in our patients, megaloblastic changes and an impaired maturation were detected, vitamin B_{12} (Cases 1 and 3) and citrovorum factor (Case 2) were given. Citrovorum

factor did not affect the disease. Vitamin B_{12}, on the other hand, corrected the megaloblastic changes and the granulation defects of the neutrophils, but it did not appear to be of benefit in the management of the disease.

2. It is a well-established fact that, in childhood especially, corticosteroids and ACTH frequently will induce remission of acute leukemia. These agents have, in addition, the ability to control the hemolytic processes and the hemorrhagic manifestations which very often accompany the leukemic processes. Two of our patients (Nos. 1 and 3) were given prednisone in high doses (30 to 40 mg. per day) throughout the course of their disease, or ACTH (25 units per day, intravenously). The impression was that the hemolysis was diminished, at least to a limited extent, and that the hemorrhagic manifestation in one of the two cases was temporarily controlled. These drugs were also found to be of some use for their antiasthenia effect. They did not, however, induce remissions or affect the main pattern of the disease.

3. The folic acid antagonist, Methotrexate, and purine antagonist, 6-mercaptopurine, were used in Case 1 and Case 3. In the latter, some changes were noted in the absolute number of cells in coincidence with the administration of these drugs, but, as already stated, the evaluation is extremely difficult. They failed, however, to induce temporary remission.

4. An alkylating agent, chlorambucil, was used in Case 1. The concept guiding our choice was the knowledge of its activity against cells of the reticuloendothelial system. The involvement of this system in the disease and the cytological characteristics of most of the immature erythroid elements resembling histioid cells suggested the use of this drug. No effect was produced on the progress of the disease. A possible fleeting effect upon the number of circulating "blasts" was noted after a high dose (0.420 mg. per kilogram per day) of chlorambucil was administered (Fig. 5).

SUMMARY

Clinical histories of two children with acute erythromyelosis and one child with acute erythroleukemia are reported and the difficulty of differential diagnosis considered.

The hematological and clinical findings are evaluated and followed throughout the patient's course.

The pathogenic mechanisms of the anemia are discussed.

A specific phagocytosis against nucleated red cells is documented.

The anaplastic and dysplastic changes of the erythroid system, the invasion of multiple organs, and the logarithmic progression of pathological cells in the blood stream (observed in Case 1) suggest strong similarity between erythromyelosis and the neoplastic diseases.

Various lines of therapeutic approach are described.

Grateful acknowledgment is made to Dr. John M. Craig for the "Pathological Diagnoses" utilized in this report, and to the nurses and Clinical Staff who assisted in the collection and organization of the material.

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X-IRRADIATION EFFECTS ON THE HUMAN FETUS*

ROBERTS RUGH, PH.D., NEW YORK, N. Y.

RADIATION insult is immediate, but the biological manifestations may be long delayed. Therapeutic irradiation of the pregnant woman can cause microcephaly and other anomalies as well as long-term subtle sequelae in the child. We now have some information relative to the stage in development and the exposure level which will cause demonstrable anomalies. We do not know the lowest level of exposure which will produce the more subtle effects.

Our evidence comes from controlled experiments with mammals other than man, and from some incidental and accidental human fetal exposures. When one plots the sequence of organogenesis in the mouse or rat with that of the human embryo, using the two time scales, it is obvious that the development of these mammalian forms is basically similar.[9] (Table I and Fig. 1.)

Every irradiation-produced anomaly in the human fetus has been experimentally produced in the mouse or rat embryo following irradiation at a comparable stage of development.[7] It is justifiable, therefore, to extrapolate from the mouse or rat to the human in regard to the specific organ susceptibility periods with the proviso that any statement is prefaced with the word "probable." However, since there is a time differential factor of

TABLE I. CORRELATIONS IN DEVELOPMENT: MOUSE AND MAN

AGE IN DAYS: EMBRYO			
MOUSE	MAN	MM. LENGTH	DEVELOPMENTAL STAGE IN HUMAN: ORGAN PRIMORDIA
5	11		Implantation
8	20.5	(1.5)	Primitive streak, blood islands, neural groove
9	25.5	(2.4)	Primordia of sense organs, thyroid, limbs, muscles, pronephos, branchial arches. Extra embryonic vasularization
10.5	28.5	(4.2)	Gastrointestinal tract + derivatives, meso-metanephros, 31 somites, yolk hemopoiesis. Abundant neuroblasts
11.5	33.5	(7.0)	Genital ridge, spleen + bronchial buds, cardiac septa, 38 somites
12.5	36.5	(9.0)	Bilobed thyroid, nerves + ganglia differentiating
13.5	38.0	(12.0)	Sexless gonad primordia, liver hemopoiesis, brain flexures, limbs, thymus, gastrointestinal tract actively differentiating
14.5	47.0	(17.0)	Cerebral hemispheres, corpora striatum, thalamus, spleen, blood vessels all actively differentiating
15.5	65.0	(40.0)	Cerebral cortex, intestinal, villi, thyroid follicles, first ossifications, sex differentiation
16.5	84.5	(78.0)	Ossification spreading, muscles functional, neuroglia in brain differentiating

Note: Highly radiosensitive neuroblasts present throughout the embryo and fetus from about day 25 until some time after birth of human.

From the Radiological Research Laboratory, Columbia University.

*Based upon Panel Discussion, American College of Surgeons, Atlantic City, Oct. 14, 1957.

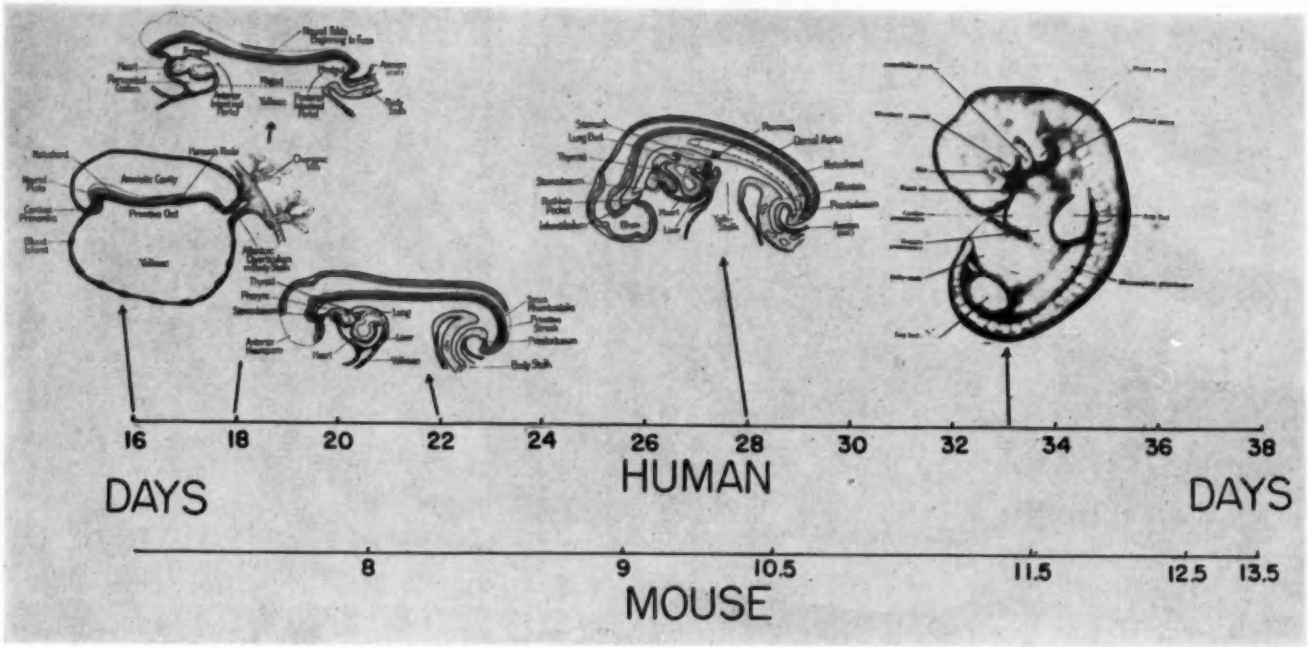

Fig. 1.—Most irradiation-critical stages in human and mouse development. (Drawings of the development of the human embryo are taken from Patten, B. M.: Human Embryology, 1953, ed. 2, Courtesy of Blakiston Div., McGraw-Hill Book Co., by permission of the author.)

about 13, the period of greatest sensitivity in the human is likewise extended. Thus far we have found no exceptions in the extrapolations. Further, in experimental studies on the mouse[20] it seems evident that effects on the embryo or fetus are direct and not mediated through the mother. There is some evidence that pregnancy actually gives the mother better survival value,[13] at least until delivery.

Table II. Major Abnormalities Found in the Mammal (Human, Rat, Mouse) Following Fetal X-irradiation

BRAIN	EYES	SKELETON	MISCELLANEOUS
Anencephaly	Complete absence	Uniform reduction: stunting	Situs inversus
Porencephaly	Microphthalmia	Reduced skull dimensions	Hydronephrosis
Microcephaly	Microcornea	Vaulted cranium	Hydroureter
Encephalocele	Coloboma	Narrow head	Absence of kidney
Reduced medulla	Narrow iris	Cranial blisters	Degenerate gonad
Cerebral atrophy	Absence of lens	Spina bifida	Atrophy of lower extremities
Mental retardation	Open eyelids	Reduced and deformed tail	Cutaneous depigmentation and hyperpigmentation
Idiocy	Strabismus	Overgrown and deformed feet	Motorial disturbances of extremities
Deformities:	Retinoblastoma	Digital reductions	Increased probability of leukemia
Narrow aqueduct	Hypermetropia	Abnormal limbs	
Hydrocephalus		Syndactyly	
Rosettes in cortex and medulla		Brachydactyly	
Dilation of third and lateral ventricles		Odontogenesis imperfecta	
Neuroblastoma		Exostosis on proximal tibia	
Herniated brain		Metaphysis	
		Amelogenesis	

Implantation of the human ovum takes place at about day 10 or 11 after insemination.[10] Radiation tolerance during this preimplantation period is not known. The most radiosensitive period in the entire prenatal life of the human probably occurs from about day 18 through about day 38, immediately following implantation. After day 38, higher levels of exposure are necessary to produc anomalies. This is because during this earlier period there is a great abundance of embryonic cells in their most radiosensitive stage. It is now believed that an exposure of as little as 40 r to the embryo on about day 28 might conceivably produce serious abnormalities. Irradiation of the rat embryo at a comparable stage has caused anencephaly or total absence of brain.[6] Such monstrosities can come to term, but cannot survive. It is during this period that all of the organ primordia are laid down by rapid differentiation from primitive cell types.

We know that the adult neuron can tolerate an exposure of 10,000 r, the embryonic neurectoderm can tolerate only about 400 r, while the transforming neuroblast can tolerate no more than 40 r.[5] The most radiosensitive stage in the etiology of a cell is during the transformation from its embryonic to its adult stage, whether it be a neuroblast, myoblast, osteoblast, or erythroblast.[14, 15] During this embryonic period of about day 18-38 such transformations are occurring in almost every one of the tissue varieties of the human embryo. One might suspect

that fractionation of exposure might reduce the incidence of malformations, but this is not so.[1] Actually the severity of embryonic defects is far greater in response to fractionation than to a single dose, probably because more organ primordia will be radiation-insulted during their respective critical stages of development. As has been pointed out,[22] this is also the period during which neither the woman nor her clinician might suspect a pregnancy. (Fig. 2.)

It can be assumed that high energy x-irradiations may be rather uniformly distributed throughout the embryo or fetus, which is a mosaic of actively differentiating cells and likewise a mosaic of varying sensitivities. Irradiation destruction is proportional to the number of radiosensitive cells, but the specific anomaly produced is related to the differentiating organ system(s) possessing such cells. During the period of most active differentiation one would expect to produce the maximum possible damage even with low level exposures. At later stages in development higher exposures are necessary to produce gross abnormalities. This in no way implies any linearity in fetal radiosensitivity. There are exposures below which *detectable* anomalies are rare. Effects are qualitative

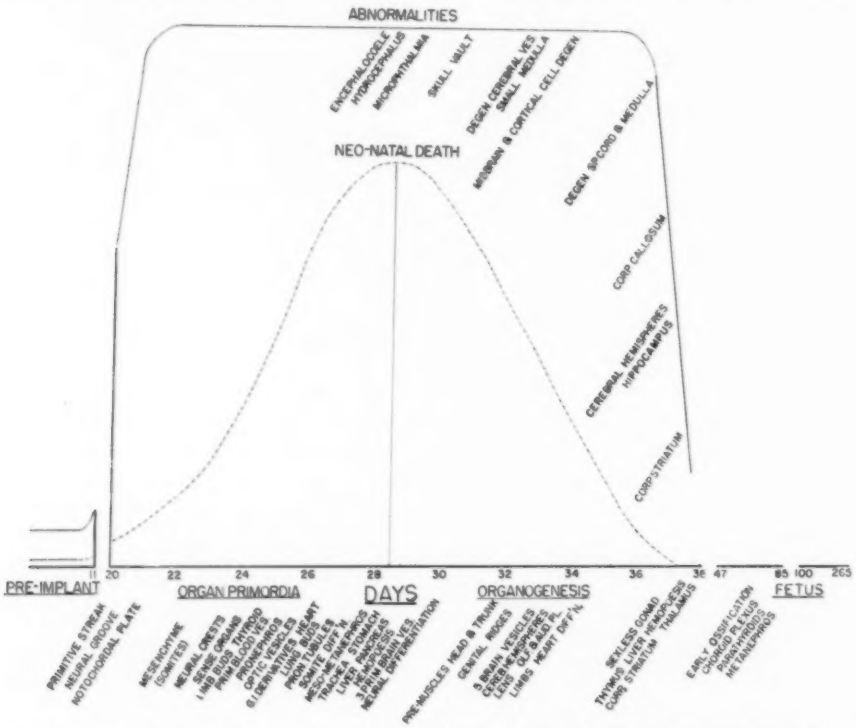

Fig. 2.—Time schedule of human organ primordia and irradiation-induced anomalies. This graph is a composite, based upon a similar graph for the mouse by L. B. Russell (1954) and such data as are available from normal human embryology (Patten, 1946) and from some human irradiation data. Microphthalmia, for instance, appears if the irradiation occurs while the optic vesicles are in active differentiation, about day 26.

rather than quantitative. However, one who is acquainted with the chronology of human development can predict rather accurately the types of anomalies to be expected following fetal exposure at any specified time, due simply to the presence of the dynamic and metamorphosing precursors of specific organs. After about day 40 the organ systems are largely established and gross teratologies can, but are less likely to, occur except at higher levels of exposure. However, the clinician should be cautioned in regard to possible fetal irradiation at any time for three basic reasons:

1. Wherever the primitive *germ cells* arise they will be highly sensitive to ionizing radiations. It is likely that they are at least as sensitive, if not more so, to radiation-induced mutations as are the adult germ or somatic cells. A mutation produced in such a single stem cell will multiply into all of its cellular progeny so that many functional gametes will be affected. The genetic effects of irradiation probably begin shortly after about day 32 when the genital ridges first appear, and continue through the reproductive life span of the individual. "The most precious asset of mankind today is the germ plasm which has enabled him to develop the culture we all enjoy. If current developments—of which increasing exposure to ionizing radiations is one—threaten the integrity of this germ plasm and are paving the way for the decline of our species, then here is a problem equal in magnitude to any with which we are currently confronted."[8]

2. The onset of teratological effects of x-irradiation is probably about day 18 in the human embryo, simultaneous with the development of the *neural groove*, the precursor of the *central nervous system*. During the next few weeks the neural axis and primary brain are organized. As the various organ systems develop they become invested with neural components, emanating from this growing central nervous system. These neuroblasts are among the most radiosensitive of all cells, and since they are found throughout the embryo and fetus, radiosensitivity is widespread. Irradiation of neuroblasts to 40 r, wherever they are found, usually results in their necrosis and death, with the consequent neural deletions. Such deletions will be the more obvious and widespread the earlier the developmental stage irradiated. There is undoubtedly functional damage at levels too low to be manifest by any histopathological test. Microcephaly, a common sequela of fetal irradiation, may not be apparent upon histological examination regardless of the degree of neural loss. The brain may be a miniature of the normal, uniformly deficient in neural elements. Some 64 per cent of the children exposed in utero to atomic bomb radiations within 1,200 meters, and who appeared normal at delivery, showed microcephaly with mental retardation by 4.5 years of age. There was no microcephaly among the 194 similar pregnancies beyond the 1,200 meters.[12] "Among 30 women who were pregnant at the time, who were within 2,000 meters of the hypocenter at Nagasaki, and who bore signs of radiation exposure, there resulted 7 fetal deaths (23%), 6 neonatal and infant deaths (26%) and 4 instances of mental retardation (25 %) among the 16 survivors (53%). The overall morbidity and mortality

was 60%."[26] Mothers within the same 2,000 meters but without radiation exposure signs had over-all mortality of offspring of only 10 per cent, and, in distant controls, it was 6 per cent. It is believed that irradiation-damaged cells cannot recover, but since the fetus also possesses many early undifferentiated and less radiosensitive embryonic cells, it has remarkable powers of topographical regeneration and repair following phagocytosis of the irrevocably damaged cells. However, regeneration is never complete and the neural deletions which result are responsible for the microphthalmia, microcephalia, neural insufficiencies, and other nervous disorders which often follow fetal irradiation.

3. It is now known that prenatal irradiation increases the probability of *leukemia* in young children, even though a linear relation is yet unproved. "The dose of irradiation received by the fetal gonads during diagnostic pelvimetry frequently exceeds 2.5 r. The present investigation suggests that, besides causing genetic damage, this apparently harmless examination may occasionally cause leukemia or *cancer* in the unborn child."[24] A study of some 1,400 children showed that the probability of leukemic death was doubled in those who had had fetal irradiation. The latent period of this and other cancer developments may be years or decades, but until disproved it can be presumed that carcinogenesis is initiated more readily in the more radiosensitive embryonic cell, particularly when the entire fetus is exposed and thereby rendered physiologically more susceptible.

There have been references in the literature to instances of fetal x-radiation which were not followed by gross anomalies, or human embryos which survived large exposures, came to term, and appeared to be "normal" by all pediatric tests. Three things must be said about these cases: First, As the fetus advances in age it is better able to avoid gross teratologies following x-irradiation. However, radiation tolerance, in terms of a specific number of roentgens at various fetal ages, has no meaning because some anomalies can be produced by irradiation at almost any prenatal period. Specific teratologies undoubtedly have varying thresholds at specific developmental moments, but cannot be quantitated. Second, Irradiation-damaged cells are phagocytized, and the fetus can, through limited reorganization of the remaining undamaged cells, maintain rather normal topography. Third, With advanced fetal age, damage to the scattered neuroblasts cannot be as readily detected. However, there is histopathological evidence of such effects.[3, 4] In some cases, while there was no detectable evidence of damage at birth, following fetal irradiation, there has been subsequent evidence that the child exhibited abnormal psychological behavior. This supports the thesis that there may be functional damage at levels too low to have structural corollaries. There can be no controls for these data. The range of human "normality" is so great, so inclusive of a large variety of debilities, that even if a child's potential I.Q. is reduced from 140 to 70 by fetal irradiation, he would still be considered as "normal." Without elaboration, reference is made to two recent cases reported in the literature where mental and other conditions were directly attributable to fetal irradiation.[2, 11] There are sequelae to fetal

irradiation which are not evident for many years, even besides the genetic mutations which affect future generations, such as the shortening of life, the development of cancer and cataracts, sterility, the increased susceptibility to disease, and numerous subtle and less evident factors which affect survival.

In conclusion, the embryo, particularly between days 18 and 38, and the later fetus, represent the most radiosensitive stages in the life of human beings, due largely to the presence of actively differentiating cells involved in organogenesis. During certain periods of development, monstrosities in the offspring may be produced by low level therapeutic or even diagnostic exposures of the pregnant woman. Teratologies are less likely as the embryo becomes a fetus and are never formed by irradiation of the fully developed adult. Nevertheless, the damaging effects of ionizing radiations become more subtle with advancing fetal age and may well produce viable but psychologically ill-adjusted individuals, the like of whom are currently contributing to our overcrowded institutions. As Hicks[5] has written, "From the social viewpoint it is probable that the production of an individual with a subnormal brain may be a worse catastrophe than one with almost no brain."

We simply cannot evaluate the deleterious effects of diagnostic and therapeutic irradiation of the fetus.

The x-irradiation of the pregnant woman, particularly in the early trimester, should be discouraged under all conditions, short of saving the life of the mother. Further, it would be a wise practice to determine the time of the prior menses in all radiological examinations of women in order to avoid the possibility of exposure of an unrecognized pregnancy during the most radiosensitive period at about 2.5 to 6 weeks.

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A physician's first duty is to his patient; his second only, to himself.

All quackery reverses this principle as its fundamental axiom. Every practitioner who reverses it is a quack. A man who follows it may be ignorant, but his ignorance will sometimes be safer than a selfish man's knowledge.

From an ADDRESS BY OLIVER WENDELL HOLMES, M.D., delivered in 1858 to the Medical Graduates of Harvard University, the Boston Medical and Surgical Journal.

MANAGEMENT OF BRONCHIAL ASTHMA IN CHILDREN

LEON UNGER, M.D.,* A. ALVIN WOLF, M.D.,** JAMES H. JOHNSON, M.D.,* AND DONALD L. UNGER, M.D.***
CHICAGO, ILL.

WHEN a child is brought to a physician the diagnosis is the first consideration. The term "asthma" has been somewhat confusing because it has been applied to any condition in which wheezing occurs. Chevalier Jackson[1] long ago said that "all is not asthma that wheezes," and his statement has been corroborated by many others, including ourselves.

We do not like the loose term "asthma." We prefer the words "bronchial asthma." To us, bronchial asthma is an allergic condition characterized by wheezing, dyspnea, orthopnea, and cough. It is usually preceded or associated with seasonal or perennial rhinitis, and with partial obstruction of the lower air passages.

We believe that all patients with true bronchial asthma are allergic. It is true that we cannot always demonstrate the causative allergen or allergens, especially in patients in whom the asthma has begun after the age of 40. In children the discovery of the allergen is almost always a comparatively simple matter. In 1952, for example, we obtained positive skin tests in 362 of 366 asthmatic children.[2]

*From the Northwestern University Medical School and Chicago Wesley Memorial Hospital, Chicago, Ill.

Address: 185 North Wabash Ave.

**From the University of Illinois School of Medicine and Michael Reese Hospital, Chicago, Ill.

***From Michael Reese Hospital, Chicago, Ill.

Time will not permit an adequate discussion regarding the allergy survey. Needless to say, a good history will often unearth the symptoms and may even elicit the causative factor, e.g., ragweed or cat hair or eggs. The history must concern itself not only with possible allergic factors, but also with illnesses from the time of birth, with emotional problems, and with details as to previous immunizations.

The physical examination must be thorough, from head to foot, with special attention to the lungs and heart, as well as the nasal passages. Fluoroscopic examination of the chest follows, and x-ray films of the chest if findings seem suspicious. We carry out a complete blood count in each case, also a Kahn test, nasal smear, urine and sedimentation rate.

SKIN TESTS IN CHILDREN

Skin tests in children are so important as to warrant some discussion.

a. *Indications.*—Skin tests are indicated in almost all allergic conditions, especially bronchial asthma, hay fever, perennial allergic rhinitis, atopic dermatitis (eczema), and gastrointestinal allergies. They are usually useless in urticaria and migraine.

b. *Timing.*—Tests can be done from birth but we usually see our patients

after the age of 2. We have done tests in children as young as 9 months, but skin reactions in infants are usually milder than in older children. Tests may be negative in asthmatic infants and positive in these same children when the tests are repeated a few years later.

c. *Location of Tests.*—In infants and young children we are forced to use the back or chest. In the older children we do the tests on the arms, as in adults.

d. *Number of Tests.*—Important allergens may be missed if tests are done incompletely. One should test with all possible inhalant materials and also with those foods which the child eats. Some physicians do about 20 to 30 skin tests and consider that they have carried out a proper allergy survey. In many children this small number of tests is insufficient and poor results are apt to occur.

e. *Scratch and Intradermal Tests.*—Tests in children (and in adults) should first be done by the scratch method. This technique is safe and easy to perform, and children rarely complain. In fact, many enjoy these tests, especially if they are done on the forearms so that they can be seen by the child. Positive reactions can be obtained in about 75 per cent of asthmatic children. About 60 scratch tests can be done in one sitting.

Intradermal tests *must* follow if the scratch method has not yielded sufficient information. In children we usually do 20 to 25 tests by this technique and all at one sitting. Most of these intradermal tests are made with important inhalant extracts, e.g., pollens, fungi, house dust, animal, and miscellaneous derivatives. Food extracts are also used if the history is suspicious. If not, we omit intradermal food tests because reactions with food extracts are not nearly as accurate as with inhalant materials.

The combination of scratch tests first, followed by intradermals where necessary, yields at least 95 per cent of positive skin tests in asthmatic children. Those who do only scratch tests can expect not more than 75 per cent results. Those who do only intradermal tests are also wrong because (a) they are apt to bring on systemic reactions which might even be fatal, (b) they do fewer tests and thereby are likely to miss positive skin tests, and (c) intradermal tests are more painful.

f. *Precautions.*—Our patients have strict orders to avoid, for at least 48 hours, certain drugs which lessen skin test reactions. These drugs belong to the sympathomimetic group, e.g., ephedrine, epinephrine, and certain nasal sprays or drops, or the antihistaminics or combinations which contain them.

g. *Laboratory Skin Tests.*—Tests done by commercial laboratories, with perhaps a few exceptions, are apt to be misleading because the results of skin tests must be correlated with the history of exposure and with clinical trials. Some laboratory reports are very poor, and they may wrongly accuse such materials as paper or aspirin. In addition, if the patient is dermographic the reports are apt to show positive reactions to almost all the materials. In patients with severe dermographia the allergist usually resorts to the passive transfer technique. If the scratch and intradermal tests are both negative, the allergist will often

continue tests by dropping pollen or fungi into the conjunctival sac or the nasal passages. Commercial laboratories do not carry out these techniques.

From the practical point of view, physicians who refer allergic individuals to commercial laboratories are usually given a list of positive skin tests, with little or no recommendations as to therapy. The physician is apt to be bewildered, especially if the number of positive reactions is large. Unless he is well trained in the field of allergy, the physician is then tempted merely to treat symptoms as they occur; he may not give the child the hyposensitizing injections which lead to an increase in resistance to the allergenic materials.

If, however, the child is referred to one who is interested in allergy and equipped to do thorough testing, the referring physician can have his patient sent back to him, along with a detailed written report. Solutions for hyposensitization (if indicated) will accompany the child, along with instructions as regards dosages. Suggestions for avoidance of primary allergens and secondary factors will be outlined in the report. The child will be asked to return to the allergist at intervals. Such cooperation between the referring physician and the allergist usually leads to good results. We strongly recommend this procedure for the pediatrician who is too busy to carry out thorough allergy surveys.

Children rarely outgrow bronchial asthma. We cannot emphasize this too strongly. Infectious types of asthmatic bronchitis tend to disappear, but the allergic types usually culminate in true bronchial asthma. Delay in allergy surveys, including skin tests, is apt to be followed by chronic asthma with emphysema and deformed chest.

TREATMENT

Therapy must be discussed under three headings: Specific, Symptomatic, and Preventive.

I. *Specific Therapy.*—

The specific management of asthmatic children consists of avoidance of causative allergens, with or without hyposensitization. This combination undoubtedly gives much better results than can be obtained from any kind of nonspecific therapy, e.g., psychosomatic, antibiotic, vaccines or ordinary medications.

A. *Avoidance* must be as thorough as possible. All causative allergens must be removed or avoided, even if the favorite cat or dog is to be taken from the home. In all of our patients with all-year-round symptoms of bronchial asthma and/or rhinitis, we urge the following:

1. The home must be spick and span from the allergic point of view.

2. All pillows in the entire home are to be either rubber or Dacron. Other types, including feather, kapok, or cotton, are to be permanently removed. They are not to be stored in the attic or in some closet, to be brought out for guests. This order includes "show" pillows in the living room or den.

3. All mattresses in the home are to be made of rubber, or are to be encased in zippered plastic material.

4. Rug pads are to be rubber or are to be removed. We urge floor coverings which are easily cleaned, e.g., tile, stone, or linoleum. Furniture should be rubber-filled, if at all possible.

5. No household pets are allowed in the home. These include cats, dogs,

canaries, and parakeets. Stuffed bed toys, e.g., Teddy bears, are forbidden.

6. Dusting is to be done by vacuum cleaners with attachments or by wet mop. Whisk brooms only push dust from here to there.

7. Basements are to be kept as dry as possible. Wet or damp basements are usually moldy and molds are important allergens.

8. The home itself should be located in as clean a neighborhood as possible. If the neighborhood is close to railroad tracks or to industrial fumes or gases we usually advise a change of address.

9. Allergy to a food is frequently proved by the history and by several clinical trials. In such cases the skin tests are usually positive. If this allergy to a food has thus been verified, that food should be avoided. The child must avoid not only eggs, for example, but all foods which contain egg, e.g., mayonnaise and certain cakes and puddings. Avoidance of some foods for some months may by itself bring about a degree of hyposensitization. Other foods, e.g., fish and nuts, are so potent that the sensitive individuals usually must avoid them for the rest of their lives.

Cooking of foods lessens the danger of symptoms. Hard-boiled egg and powdered milk, for example, are less allergenic than the raw food. This fact permits some less-allergic individuals to indulge in the cooked variety of foods.

Botanical relationships must not be overlooked. Certain foods belong to groups, e.g., the legumes (pea-bean) family, or the gourds, e.g., pumpkin, squash, or cantaloupe. Cauliflower, broccoli, and Brussels sprouts are closely related. Patients who are definitely sensitive to one food of a group must avoid or look with suspicion on other members of the group.

Skin testing with food extracts is very reliable for a few potent foods, e.g., fish, eggs, nuts, celery, and cottonseed. In sensitive individuals allergy to these foods is usually easily demonstrated by the scratch technique. One *must* prove allergy to foods by withdrawal of the suspected food and then by cautious trial. It is wise to prove such tests at least three times. The intradermal food reactions are often misleading.

All this brings to mind the case of an 8-year-old boy whom we first saw about a year ago. He had a history of perennial asthma almost since birth, along with recent hay fever. He had been skin-tested by the intradermal method; many positive reactions had been found to foods and to inhalant materials. Hyposensitization with the inhalant extracts was correctly given but, in addition, all the positive-reacting foods were forbidden this child. He was not allowed milk, chocolate, and many other foods. As a result the child came to our office weighing less than 50 pounds and he was almost skin and bones. His spirits were low because he was not allowed to play with other children when he had asthma and he had asthma most of the time.

We carried out skin tests by the scratch tests, followed by about 20 intradermal tests with milk, chocolate, and inhalant materials. We found that skin tests for foods were practically negative. We personally made him drink large glasses of milk and eat large amounts of chocolate ice cream. We continued injections of house dust,

pollens and fungi, to which he is clinically allergic; we advised continuation of precautions against house dust, household pets, etc.

The results have been excellent. This boy has gained more than 10 pounds this past year; he has very little asthma; his appetite is excellent; he plays with other boys and recently was very proud because he broke a finger while playing baseball.

This case is just one of many in which allergists and other physicians have harmed their patients by relying on skin tests without regard to the fact that clinical allergy to these foods was not proved. We may forget that children need much food to live and to grow.

B. *Hyposensitization* (densensitization) consists of injections of increasing amounts of extracts of important allergens which cannot be avoided, e.g., house and occupational dusts, pollens, fungi, feathers, or animal danders. Results are usually good, especially when combined with as thorough avoidance of allergens as humanly possible. Actually, failure is rare as good to excellent results can be obtained in almost all asthmatic children.

Hyposensitization must be continued for long intervals. The minimum is at least a year and, in many cases, injections must be given for several years. Allergists vary to some extent on this point. We believe that injections should be continued until the patient is symptom-free or almost symptom-free. Then injections are stopped, but the patient or parent is warned that symptoms may return. Strict avoidance of causative allergens must continue as carelessness may result in recurrence of asthma. If symptoms do return after an interval of 3 to 10 years we advise complete re-testing. The child may have overcome certain allergens but may have acquired new ones. One must remember that an asthmatic person has an allergic foundation and therefore has the ability to change his sensitivities.[3]

II. *Symptomatic Therapy.*—

The symptomatic therapy of bronchial asthma is nonspecific and one should not expect any more than temporary relief of symptoms. The measures used, including the new corticosteroids, can only hope to lessen or eliminate the asthmatic symptoms as they occur.

Reassurance is the most important single measure, especially if the child is having his first severe attack. The calm confident manner of the physician usually exerts a very soothing influence on the frightened child and the rest of the family. The physician immediately informs everybody that the attack will be overcome within a relatively short time.

Medications are used according to the severity of the attack. For mild to moderate symptoms repeated subcutaneous injections of 1:1000 epinephrine in doses of 0.10 to 0.20 c.c. usually suffice, along with 5 to 10 drops of a saturated solution of potassium iodide. If necessary, a mild sedative may be added, e.g., elixir of Benadryl. This combination is almost always effective.

For more severe asthma, the epinephrine may be injected every 4 hours; we often add 0.10 c.c. of Sus-Phrine, a long-acting epinephrine suspension. Instillation of 5 grains aminophylline rectally is helpful and we prefer this to aminophylline suppositories. In addition, a teaspoonful

of syrup of ipecac will induce vomiting, and as the child vomits he usually eliminates sputum which he has not learned to cough up in the manner of adults. Some physicians also add ephedrine by mouth.

For the most severe cases (status asthmaticus) one must usually add antibiotics, e.g., penicillin, because almost all such cases have an infectious complication which causes symptoms to continue. This diagnosis is easily made by the finding of crepitant râles as well as wheezing, also by leukocytosis, some fever, an increased sedimentation rate, and perhaps by some cloudiness in a chest x-ray film.

Hospitalization is urged for these severely ill children. Removal from the home is usually beneficial because it lessens the factor of inhalation of allergens, e.g., feathers, house dust, and animal danders. In addition, change to a hospital may be of striking benefit because of psychological factors, especially removal of the child from overprotective parents. At the hospital one can carry on investigative work, e.g., chest x-rays, blood counts, and tests of sputum for sensitivity to antibiotics. Bronchoscopic aspirations may be necessary and may be life-saving; a nonopaque foreign body in a bronchus, e.g., peanut, pea, or bean, may be the cause of bilateral wheezing, as in a 3-year-old child recently admitted to our hospital.

Sedation in all asthmatic patients should be mild, e.g., an antihistaminic drug or aspirin. We never give morphine or Demerol to patients with asthma.

At our hospital, the Chicago Wesley Memorial, we have 12 beds for asthmatic patients. These rooms have air filters in the windows and beds with rubber or Dacron pillows and with rubber mattresses. The floor is covered with linoleum, the chairs synthetic leather, the curtains light and frequently washed. In each of these rooms there is a sign which states that feathers, flowers, and smoking are forbidden. The floors are cleaned with a wet mop.

Patients who are allergic to inhalant materials usually clear up very rapidly in such rooms. This is a fact which helps in discovering the cause of the asthmatic attack. If the asthma does not lessen in 2 to 3 days, one must question the diagnosis, or must search for other factors, e.g., allergy to foods, or some infectious process, a psychogenic influence, or a foreign body.

ACTH and prednisone have become very important. Cortisone itself is rarely used any more. In severe cases, especially in the older child and in adults, we usually start a continuous intravenous drip. Each liter of 5 per cent glucose in water contains aminophylline (about 0.25 to 0.50 Gm.) and about 10 to 20 units of soluble ACTH. The drip is continued at the rate of 2 to 3 liters per 24 hours, and this is stopped when the asthma is overcome. The child is then given intramuscular injections of ACTH-gel in doses of about 20 units per day, gradually reduced, and then stopped. In a few obstinate cases it may be necessary to temporarily substitute 5 to 10 mg. prednisone per 24 hours. In some cases the intravenous drip will not be necessary. The ACTH-gel can be injected intramuscularly.

These corticosteroids have been of great help in lessening asthmatic symptoms, but one must remember that they

are not without danger, and they do not cure asthma or any other disease. The child must still be given the benefit of a thorough allergy investigation, including complete skin tests, followed by careful avoidance of causative allergens and by hyposensitization, if necessary.

Time will not permit even mention of many other available drugs, but those we have discussed are the important ones.

We would like to emphasize that asthmatic children should be as active as other children, but to the point of their breathing capacities.

Prevention of Asthma.—

Children of allergic parents frequently develop allergic conditions, including bronchial asthma. It is estimated that if both parents are allergic about 60 per cent of their children will become allergic, and about 30 per cent if only one parent is allergic.

Much can be done to lessen the chances for development of allergic symptoms in these children. Such homes should be as dust-free as possible, and they should be free from dogs, cats, feathers, kapok, and stuffed animals.

New foods should be tried one at a time, at least a week apart, to see if symptoms occur. A feeding of raw egg may be disastrous. Cooked foods are less allergenic than raw.

If mild symptoms develop, e.g., "eczema," hay fever, sniffles or recurrent bronchitis, we advise a prompt and thorough allergy survey, including complete skin tests.

Such children should be guided away from dusty occupations, e.g., farmer, furrier, baker, upholsterer, grain mill worker, florist, sandblaster, miner, or domestic.

Exposure to "colds" should be minimized.

Psychosomatic factors, if present, need proper attention.

The above precautions are important, and, if carefully followed, the onset of severe asthma in these children can be prevented, or if asthma does occur the symptoms can easily be controlled.[4, 5, 6]

The Allergy Foundation of America has now come into being. It is doing an excellent work in educating physicians and the laity and is now supporting research problems. All pediatricians should join and give a helping hand. We know a great deal about allergic diseases, including asthma. We can distinctly lessen the suffering of allergic patients.

The Jewish National Home for Asthmatic Patients in Denver, The National Foundation for Asthmatic Children in Tucson, and the Asthmatic Childrens Aid in Chicago are also of great help in this field.

DISCUSSION

In these few minutes we have briefly discussed the management of bronchial asthma in children.

In 1952, we reported our results,[2] as shown in the accompanying Table I.

We believe our results have been good. They have been even better since the introduction of ACTH and the steroids. We are not satisfied. Progress will depend on further education of the physicians and the laity. We are especially indebted to the many pediatricians who have been pioneers in the field of allergy, and who have urged early and thorough allergy surveys in suspicious cases.

The severe asthmatic child with marked pigeon breast has now become

TABLE I. RESULTS OF TREATMENT IN 306 CASES OF BRONCHIAL ASTHMA IN CHILDREN

TYPE OF ASTHMA	AGE AT ONSET	SYMPTOM-FREE		MARKED IMPROVE-MENT		MODERATE IMPROVE-MENT		NO IMPROVE-MENT		DEAD	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
I. Paroxysmal (281 cases)	Before 1	15		20		4		1		1	
	1-2	28		46		9		4		1	
	3-4	20		29		8		1		1	
	5-7	20		24		12		3		0	
	8-10	6		10		1		2		0	
	11-13	8		3		3		0		1	
	Total	97	34	132	47	37	13	11	4	4	1
II. Chronic (25 cases)	Up to 13	2	8	7	28	8	32	4	16	4	16
Total (306 cases)		99	32	139	45.5	45	14.7	15	4.9	8	2.6

almost a rarity, but we still see one occasionally, and we realize that that child has been neglected. We must renew our efforts to prevent such tragedies.

SUMMARY

Bronchial asthma is an allergic condition characterized by wheezing, dyspnea, orthopnea, and cough. It is usually preceded or associated with seasonal or perennial rhinitis.

The responsible allergens in children are easily discovered in at least 95 per cent of the cases.

The history, physical examination, and clinical trials are important.

Skin tests should be made in all cases and be done with all protein-containing materials to which the child is exposed.

Scratch tests should be done first; intradermal tests are also necessary in about 25 per cent of all cases.

Best results are obtained by strict avoidance of causative allergens and by hyposensitization with important inhalant materials.

Preventive measures are important in children of allergic parents. They can definitely delay the onset and lessen the severity of allergic conditions, including asthma.

Reassurance, epinephrine, iodides, and ACTH and steroids are the most important symptomatic measures.

Attention to complicating infections and to psychic influences are also necessary.

Results in asthma in children are usually excellent and they are improving.

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GROWTH AND DEVELOPMENT

III. Skin Color in Negro Infants and Parents: Its Relationship to Birth Weight, Reflex Maturity, Socioeconomic Status, Length of Gestation, and Parity

Carrell P. Horton, M.A., and E. Perry Crump, M.D., Nashville, Tenn.

THE study of variations in skin color within the Negro group can be approached from several points of view. These may be combined into three broad categories: namely, (1) the cultural, (2) the biological, and (3) the functional approaches.

The cultural approach to the study of skin color is related to the differential values attached to being a particular color. The reaction of both Negroes and whites to this phenomenon has been the subject of a great deal of scientific observation and speculation. It is generally conceded that color plays a prominent role in Negro life. Myers and Yochelson[1] state: "Within the Negro community, shades of color have considerable social significance, and greater opportunities for enhancement of status are offered to the light-skinned individual." In a study of the skin color judgments of Negro college students, Marks[2] found that ratings of attractiveness are definitely affected by objective skin color, or by factors associated with it. Consciousness of color has been found to exist in Negro children as well as adults. Seeman[3] found that third- and fourth-grade Negro children indicate a "commitment to the superior value of light skin." He further states that skin color differences are associated with differences in "friendship and reputational status." Negro children of preschool age were studied by K. and M. Clark,[4] and the authors conclude that the factor of skin color is an important one in the genesis of consciousness of self and racial identification. These same authors[4] make two other major points:

1. "The results show clearly that an analysis of subjects upon the basis of skin color may not assume that the difference between the medium skin color group and the light group is equal to that between the medium and the dark group in reference to the inherent dynamics involved. . . ."

2. "It would appear that the extreme groups of light and dark children are beginning to identify themselves on the basis of their own skin color, whereas the medium group seems influenced by other factors in making identifications of self."

The problems and complications which seem to arise from this cultural evaluation of skin color have perhaps stimulated interest in the biological approach to skin color. Spencer,[5] in reporting on recent advances in pigmentogenesis, stated that the discovery of an oxidizing substance capable of bleaching pigment of the skin "opens

From the Department of Pediatrics, George W. Hubbard Hospital of Meharry Medical College.

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vast possibilities which might have repercussions on our psychological pattern as well as on our social conduct."

The biological approach to skin color has many forms. One area of concern is the inheritance of skin color. Most authors agree that children of parents with mixed white and Negro ancestry do not themselves show any consistent pattern in skin color. Niedelman[6] states: "Children of families of mixed white and Negro blood show a wide variation in color, and in one family there may be one child almost white and another black." The same position is taken by Kephart[7] and by Dummett.[8] Kephart further states that the common anthropological estimate is that between 10 and 20 per cent of the Negroes in this country have no non-Negro ancestors.

The use of spectrophometric measurements for studying skin color inheritance has been reported on by Gates,[9] and appeared to him to suggest a promising line of study.

There is less agreement as to whether or not the infusion of "white blood" is contributing to the disappearance of Negroes as a minority group. Linton* has maintained that in 200 years the American Negro will have disappeared as a minority group. This is denied by Kephart, who feels that such a claim "does not appear to be either sociologically or biologically tenable." Blue[10] takes the position that we cannot prove or disprove whether Negroes are becoming lighter in color. The question is further complicated by general agreement that Negroes tend to grow darker with age, as indicated by Herskovits[11] and Niedelman.[6] Niedelman states that the pigmentation of the skin in a Negro does not reach its maximum until puberty, after which it decreases in intensity.

The functional approach to the study of skin color appears to have been neglected. Gross differences in pigmentation are explained in a variety of ways. Eller[12] states that, "Some authors attribute pigmentation to the effect of heat; others consider it to result from the combined effects of heat and humidity; while some believe that the color is due to the influence of the tropical sun or to increased oxygenation resulting from excessive exposure to solar rays." Whatever the reason for difference in color of the various racial groups, it would seem logical to ask if these differences have any practical effect.

Medically, the study of skin color differences has been made largely from a dermatological standpoint. Spencer[13] states that the dermatologist must recognize the play of colors and develop new visual patterns when examining cutaneous diseases in "colored people." Niedelman[6] reports that the skin of Negroes differs from that of white persons, "not only in structure and physiology but in its reaction to trauma and infection." He states, moreover, that, in addition to differences in the incidence of many diseases, there is also a difference in the "clinical and pathologic manifestations," which he feels is partly due to the social and economic conditions of Negro life.

Since the range of skin colors within the Negro group is extremely wide, this should afford an excellent opportunity to examine the practical effects of skin color *within* a racial group. The social significance of skin

*Cited by Kephart.[7]

color within the Negro group has been widely discussed, as have also various differences between Negroes and whites in both the physical and cultural areas. From these various postulations, the next step would appear to be an examination of physical and cultural differences, if any, within the Negro group on the basis of skin color differences. To the extent that skin color represents one of the major differences between Negroes and whites, it might be hypothesized that Negroes who approach the color of white would show some differences, physical and/or cultural, from Negroes who are of darker hue. That is, it poses the question, Are Negroes a homogeneous group with regard to some measurable traits and characteristics, irrespective of skin color differences? To our knowledge, very little attention has been given to this line of analysis.

It was the purpose of this study to measure some of the effects of skin color differences within the Negro group, by examining the following aspects of the problem: (1) the relationship between skin color and socioeconomic status, (2) the association between skin color of parents and skin color of infants, and (3) the relationship between skin color and some maternal-infant characteristics, namely: (a) length of gestation period, (b) parity, (c) birth weight of infant, and (d) Reflex Maturity Index of the infant at birth.

METHODS AND MATERIALS

Data for this study are drawn from a 5-year longitudinal study of factors influencing the growth and development of Negro infants and children. Included in this segment of the Major Study are records of 661 infants and their parents. All infants were born at Hubbard Hospital between December, 1953, and September, 1956.

Selection of Participants.—Participants in the Major Study were solicited primarily from the Obstetrical Clinic of Hubbard Hospital, and through private contacts for those expectant mothers who were receiving prenatal care from a private obstetrician or physician. Only those expectant mothers who were residents of the Nashville Metropolitan area were accepted into the study. In the early stages of the project, some few persons were enrolled immediately after delivery, rather than at some time during their prenatal period.

Skin Color.—The measurement of skin color can be made on a quantitative or qualitative basis. The quantitative method is perhaps best exemplified by the use of the color top, through which a measurement of the proportion of black pigmentation in the skin is obtained. A description of the technique is available in Davenport,[14] and discussions of advantages and disadvantages of the color top method can be found in Todd and Van Gorder,[15] Bowman,[16] and Todd and associates.[17] For the purposes of this study, the color top method was impractical, due to the relatively large number of persons to be rated in a short span of time, and therefore a qualitative (color chart) method was used.

The color chart used throughout this study consists of 9 color positions, ranging from (1) Very Light to (9) Very Dark.* No provision was made for assigning a double rating to persons who fell between two consecutive

*Color chart drawn up, and colors reproduced by Aaron Douglas (Negro artist), Professor of Art, Fisk University, Nashville, Tenn.

color positions. Each subject was given the color position *closest* to his actual color. Positions 1-3 are considered "Light," 4-6 "Medium," and 7-9 "Dark." Skin color of the mother was obtained by using the inner aspect of the arm just above the elbow. In the majority of the cases, skin color of the father was obtained by having the mother select his color from the color chart. Before this method of obtaining father's color was adopted, a collateral study was made to test the reliability of the mother's rating. The method was found to be highly reliable, and was therefore adopted as standard procedure, since the fathers are not readily available for rating by a member of the research staff. Skin color determinations of infants at birth were made on the ear lobe.

Measurements of parental skin color were obtained by the medical social worker at the time when the family was accepted into the project. Measurements of infant skin color were obtained by the psychologist within 12 to 72 hours after birth, as a general rule. Before actual skin color rating was begun, the 2 persons who later assigned color ratings performed comparative ratings on the same subjects in order to ensure as much comparability as possible between ratings of parents and infants. The chart was found to give consistently reliable results when used not only by the persons who actually made the color determinations, but also by other members of the research staff who had had no training or practice in making color ratings.

Socioeconomic Status.—The index of socioeconomic status used for this study is composed of the following items:

(1) occupation of father (or mother, where necessary), (2) education of father, (3) education of mother, (4) income of father (or mother, where necessary), (5) contract monthly rent, (6) purchase price of automobile, (7) Chapin Living Room Scale,[18] and (8) modified Sewell Scale.[19]

Information on the above items was obtained by the medical social worker, especially trained for this purpose. Information on parents' occupations and education, rent and purchase price of car was obtained through interviews, and the remaining items (7 and 8) by observation in the home. The final index consists of a scale which has a range of 0-72, allotting 9 points as a maximum value for each item in the index. High scores indicate high socioeconomic status.*

When a final socioeconomic score is obtained, each family is then automatically classified into one of the 4 broad socioeconomic groupings previously found to be the most discriminating dividing points for this particular population. The limits of these groups are:

Group I:	0-14	Low
Group II:	15-29	
Group III:	30-49	
Group IV:	50 and over	High

Medical-Social Information.—The number of gestation days was obtained from the mother's hospital record, as was her parity.

*When one or more of the 8 scalable items of information could not be obtained, or was unknown, that item was given the average point value of all of the known items. For example, if contract monthly rent was unknown (or the informant refused to give the information), and the family had a total score of 42 on the 7 other items in the Index, "Rent" was given a score of 6 (42 divided by 7), making a total score of 48. This practice was followed uniformly in order to have some rating on each of the 8 Index items.

Infant Measurements.—Physical measurements of the infants were taken between 12 and 72 hours after birth by selected members of the pediatric staff of Hubbard Hospital. Accuracy of results was verified periodically, and uniformity in technique and procedure was routinely followed. Only birth weight is under consideration here, although height, and circumference of the head and chest were also measured. No infant seriously handicapped by birth injury, congenital anomalies, or for any other cause, was included.

Reflex tests on each infant were performed by the psychologist within 12 to 72 hours after the infant's birth and, as a general rule, at the same morning hour.

RESULTS

The distribution of skin color among the subjects of this study is shown in Table I.

It will be noted that for both infants and parents, the majority of the cases are classified as "medium" in color. Proportionately more adults are considered "medium," whereas proportionately more infants are considered either "Light" or "Dark." There is no consistent association of color with sex.

TABLE I. PERCENTAGE DISTRIBUTION OF NEGRO INFANTS AND PARENTS ACCORDING TO SKIN COLOR

SKIN COLOR	MALE INFANTS N = 300	FEMALE INFANTS N = 319	MOTHERS N = 647	FATHERS N = 457
1. L	–	–	–	–
2. L *Light*	1.7	3.4	0.5	1.1
3. L	4.3	4.7	4.8	4.4
4. M	18.3	16.3	16.2	11.9
5. M *Medium*	21.3	25.4	33.4	27.5
6. M	32.3	22.9	32.6	35.6
7. D	16.3	16.3	11.3	16.0
8. D *Dark*	3.7	9.7	1.2	3.5
9. D	2.0	1.2	–	–
Total	100.0	100.0	100.0	100.0

The reflex maturity of the infant is summarized in a Reflex Maturity Index which measures the following conditions or reflexes:

1. Activity.
2. Moro reflex.
3. Tonic neck reflex.
4. Rooting reflex.
5. Muscle tonus.
6. Ability to raise head from prone position.
7. Ability to turn head from side to side.
8. Crawling or swimming movements.
9. Stepping movements.

Each reflex is scored on a 5-point scale ranging from 0 for "Absent" to 4 for "Very Marked," resulting in an index with a range of 0-36 points.

Skin Color and Socioeconomic Index.—Seeman[3] has stated that dark-skinned Negroes are found in greater proportion in the lower social class groups. This was found to be the case in our study. Table II shows the socioeconomic grouping of families according to skin color, where both parents fall into the same skin color group.

None of the "Light" parents is found in socioeconomic Group I, and none of the "Dark" parents falls into socioeconomic Group IV.

TABLE II. PERCENTAGE DISTRIBUTION OF PARENTS ACCORDING TO SOCIOECONOMIC GROUP AND SKIN COLOR*

SOCIOECONOMIC GROUP	SKIN COLOR GROUP		
	LIGHT N = 6	MEDIUM N = 266	DARK N = 14
I *Low*	-	7.9	35.7
II	33.3	44.7	42.8
III	33.3	39.8	21.4
IV *High*	33.3	7.5	-
Total	100.0	100.0	100.0

*Excludes parents who are not of the same color group.

TABLE III. PERCENTAGE DISTRIBUTION BY SOCIOECONOMIC GROUP OF PARENTS OF DISSIMILAR COLOR, ACCORDING TO COLOR OF DARKER PARENT

SOCIOECONOMIC GROUP	SKIN COLOR GROUP	
	DARKER PARENT "MEDIUM" N = 36	DARKER PARENT "DARK" N = 101
I *Low*	2.7	5.9
II	29.7	61.4
III	37.8	28.7
IV *High*	29.7	4.0
Total	100.0	100.0

Where parents are of dissimilar color, the same trend is noted (Table III).

Proportionately more families in which the darker parent is "Medium" fall into high socioeconomic categories than do those families in which the darker parent is "Dark." When both parents are "Dark," a larger percentage will be found in socioeconomic Group I, than when only one parent is "Dark."

This lends some credence to the contention of Myers and Yochelson[1] that, "Greater opportunities for enhancement of status are offered to the light-skinned individual." It also reveals the tendency of Negroes to marry within the same color group. For the 448 families for whom skin color of both parents is available, 67.4 per cent belong to the same color group; in 21.0 per cent of the cases the mother falls into a lighter color group than the father, while the reverse is true in 11.6 per cent of the cases. Where the parents fall into dissimilar color groups, the groups are at adjacent positions on the color scale (i.e., Light-Medium, Medium-Dark) in all but one case, in which a "Light" mother is married to a "Dark" male.

There is little indication that the color of one parent is more important than that of the other parent in relation to socioeconomic status. Considering only the "Medium" mothers, their distribution among the 4 socioeconomic groups is almost exactly the same regardless of whether the mother is lighter or darker than the father (Table IV).

TABLE IV. PERCENTAGE DISTRIBUTION OF SOCIOECONOMIC GROUP OF "MEDIUM" MOTHERS, WHERE FATHERS FALL INTO A DIFFERENT COLOR GROUP

SKIN COLOR	SOCIOECONOMIC GROUP				
	I (LOW)	II	III	IV (HIGH)	TOTAL
Mother "Medium"—father lighter	6.9	47.4	38.2	7.5	100.0 N = 173
Mother "Medium"—father darker	4.9	47.6	40.2	7.3	100.0 N = 82

Mean socioeconomic scores by skin color indicate only one major divergence in the scores of mothers and fathers in each skin color group. (Fig. 1). The mean socioeconomic score for "Dark" fathers is higher than that for "Dark" mothers, 26.9 as compared with 20.0. This is a statistically significant mean difference, although both scores still fall into the same broad socioeconomic group.

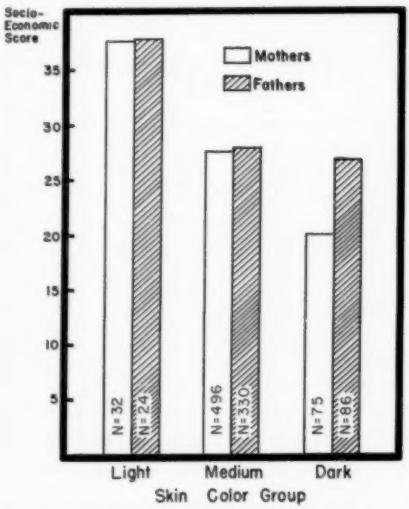

Fig. 1.—Mean socioeconomic scores of mothers and fathers, by skin color group.

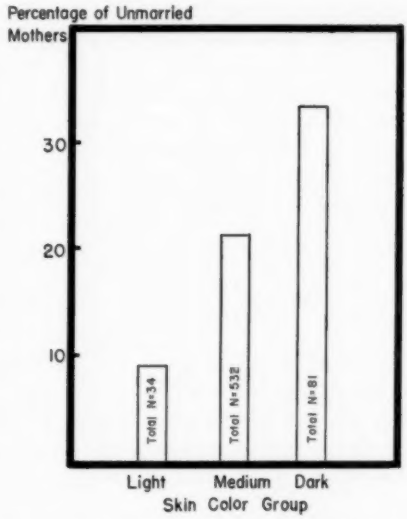

Fig. 2.—Percentage of unmarried mothers, by skin color group.

A rough indication of socioeconomic status is provided by marital status, in the case of the mother. Fig. 2 shows the per cent of mothers in each color group who are unmarried. The proportion ranges from 8.8 per cent among "Light" mothers to 32.5 per cent among "Dark" mothers.

Skin Color of Parents and Skin Color of Infant.—The unpredictability of skin color inheritance among Negroes has been discussed earlier. Kephart[7] stated that, "Negro spouses whose skin color is approximately the same shade have more chance of giving birth to children either lighter or darker than themselves than do Negro spouses whose skin color is several degrees apart." Over three-fourths (76.4 per cent) of the parents in this study who belonged to the same color group gave birth to infants who fall into the same color group as their parents. Of the remaining one-fourth, 6.3 per cent of the infants are lighter than their parents, and 17.2 per cent are darker. Over 40 per cent of the infants born to parents of dissimilar color groups are in the same color group as the darker parent, while 55.5 per cent are lighter and 3.6 per cent are darker than the darker parent (Table V).

In actual numbers, 4 of the infants born to parents of dissimilar color groups are lighter than the lighter parent, and 5 are darker than the darker

TABLE V. SKIN COLOR OF INFANTS, BY SKIN COLOR OF PARENTS, IN PERCENTAGES

SKIN COLOR GROUP OF INFANTS	SKIN COLOR OF PARENTS				
	SAME COLOR GROUP			DIFFERENT COLOR GROUPS	
	LIGHT N = 6	MEDIUM N = 264	DARK N = 14	DARKER PARENT "MEDIUM" N = 36	DARKER PARENT "DARK" N = 101
Light	83.3	4.9	-	30.6	4.0
Medium	16.7	76.9	35.7	55.6	60.4
Dark	-	18.2	64.3	13.9	35.6
Total	100.0	100.0	100.0	100.0	100.0

parent, constituting 6.6 per cent of the total number of infants born to parents who fall into different color groups. This is considerably smaller than the proportion of infants born to parents of the same color group, who are either lighter or darker than their parents (23.5 per cent).

There is little difference between the relationship of skin color of mother with skin color of infant, and that of skin color of father with skin color of infant. This is perhaps to be expected in view of the large proportion of "same-color" marriages. Sixty-six per cent of the infants are of the same color as their mothers, and 63.2 per cent are of the same color as their fathers. The correlation coefficients for skin color of mother and infant and for skin color of father and infant are 0.3001 and 0.305, respectively.

Skin Color of Mother and Gestation Period.—Previous studies have indicated that the average number of gestation days is less for Negro mothers than for white mothers. It can therefore be postulated that lighter Negro mothers would be expected to have a longer average length of gestation than would darker Negro mothers. Fig. 3 shows the mean number of gestation days for mothers in each color group. Although the average number of gestation days decreases as the darker color group is approached, none of these mean differences is statistically significant.

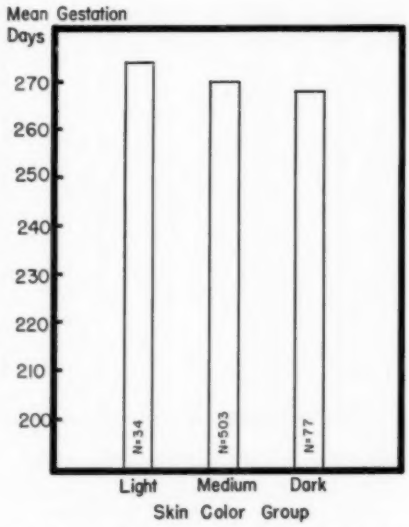

Fig. 3.—Mean number of gestation days of mother, by skin color group.

Skin Color of Mother and Parity.—Kephart[7] has stated, "It is reasonable to expect, since the differential birth rate takes the same pattern in the Negro as in the white, that the lighter-skinned Negroes have a lower birth rate than do the darker members of the group."

There is very little difference in the mean parity of mothers in this study, by skin color group. When the mean

TABLE VI. MEAN PARITY, PERCENTAGE OF MOTHERS HAVING FIRST CHILD, AND MEAN AGE OF MOTHER, BY SKIN COLOR

PARITY AND AGE	SKIN COLOR GROUP OF MOTHER			
	LIGHT N = 34	MEDIUM N = 532	DARK N = 81	TOTAL N = 647
Mean parity	2.2	1.8	2.4	1.9
Per cent having first child	20.6	27.2	19.8	26.0
Age in years	25.8	24.6	26.4	24.9

figures are rounded off, average parity is II for mothers in each color group. Actual mean figures show some slight variation which follows the same pattern as does the mean age of mothers in each color group (Table VI).

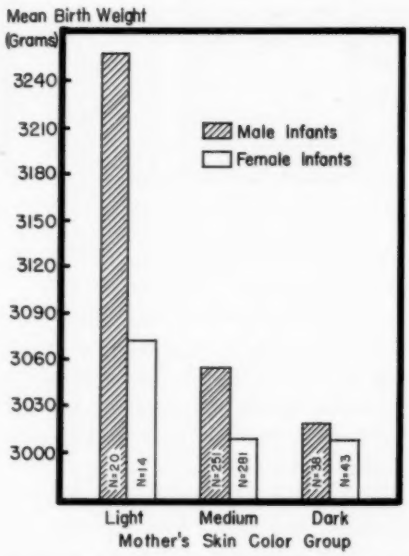

Fig. 4.—Mean birth weight of infants, by skin color group of mothers.

That is, mothers who are older at delivery also have higher average parity. The difference in average parity of "Medium" and "Dark" mothers is statistically significant. The mean age of "Medium" mothers is, however, less than that of both "Dark" and "Light" mothers. The difference in age between "Medium" and "Dark" mothers is statistically significant.

The percentage of mothers who were having their first child at the time of this study is nearly equal for "Light" and "Dark" mothers, but is about one and one-third times as high for "Medium" mothers. This is a statistically significant difference, but it too must be evaluated by taking into consideration the difference in age of "Medium" and "Dark" mothers.

Skin Color of Mother and Birth Weight of Infant.—Mean birth weights of infants by skin color of mother are shown in Fig. 4.

The difference between mean weights of infants born to "Light" mothers and infants born to "Dark" mothers is significant for both male and female babies. The correlation coefficients for skin color of mother and birth weight of infant are +0.0719 and –0.0576 for male and female infants, respectively, and are not statistically significant. Thus, there appears to be some relationship between mother's skin color and birth weight of infant when skin color is considered on the basis of color *group*, but not when the individual color ratings are used.

Skin Color of Infant and Birth Weight.—No relation is apparent between skin color group of infant and birth weight. For both male and female infants, the heaviest mean birth

weights occur in the following order, according to skin color: (1) Dark, (2) Light, (3) Medium (Fig. 5).

Skin Color of Infant and Reflex Maturity Index.—Previous studies dealing with newborn reflexes have indicated that, on the average, reflexes can be elicited from female infants to a greater degree than from male infants. Since this suggests that there is some difference among infants in the maturity of reflexes at birth, the relationship between reflex maturity at birth and other hereditary factors might logically be investigated.

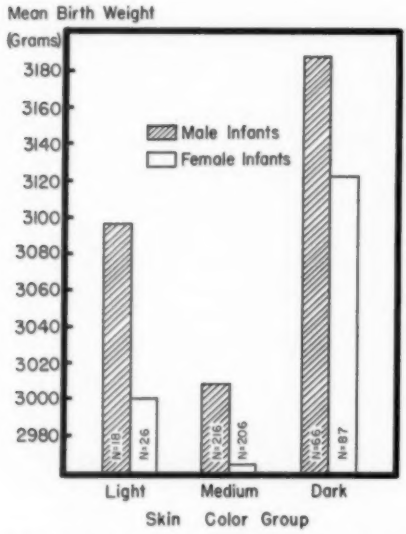

Fig. 5.—Mean birth weight of infants, by skin color group.

No relationship is apparent between skin color group and reflex maturity for male infants, but among female infants mean reflex maturity index increases as the darker color group is approached (Fig. 6).

The difference between the means of "Light" and "Dark" female infants is not, however, statistically significant, and in the absence of a corresponding trend among male infants, may suggest coincidence rather than a significant relationship.

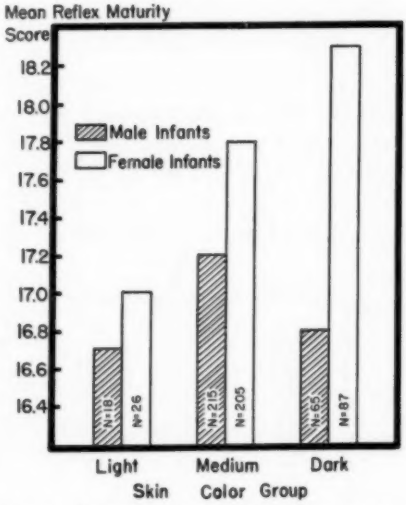

Fig. 6.—Mean Reflex Maturity scores of infants, by skin color group.

SUMMARY AND CONCLUSIONS

From data presented in this study, it is apparent that there are some areas in which specific relationships can be observed between skin color and other factors, among Negroes.

1. The social significance of skin color is confirmed not only by the greater proportion of dark Negroes in the lower socioeconomic groups (68.7 per cent of the families in which one or both parents were dark are found in socioeconomic Groups I and II, as compared with 49.8 per cent of the families in which the darker parent is medium, or both parents are medium), but also by the greater proportion of dark mothers who are unmarried. About four times as many

"Dark" mothers are unmarried as are "Light" mothers. It cannot be said whether or not the latter relationship reflects merely preferential marriage wishes, less feeling of obligation to marry women of low socioeconomic status, or some other factor or combination of factors.

2. No conclusion can be drawn concerning the inheritance of skin color from a superficial study, since the skin color of children appears to be influenced both by parents and by ancestors farther removed than parents. Results of this study indicate that the majority (in this instance, three-fourths) of children born to parents of the same color group fall into the same color group as their parents, while slightly more than half of the children born to parents of different color groups are lighter than the darker parent. There is general indication that the vast majority of Negro infants in this study are neither significantly lighter nor darker than their parents.

3. A definite relationship is seen to exist between birth weight and mother's skin color, with lighter mothers tending to have heavier babies. This relationship is evident, however, only in terms of skin color *group*.

4. Other characteristics associated with the birth of infants, specifically length of gestation period and parity, have no such clear relationship with mother's skin color. Although the mean number of gestation days decreases consistently as the darker color group is approached, the mean differences are not statistically significant. There is a significant difference in the parity of "Medium" and "Dark" mothers, but this difference is paralleled by a similar difference in the mean age of mothers in these two groups.

5. There apparently is no consistent relationship between the skin color of the infant at birth and his weight at birth, nor does his skin color appear to be significantly related to reflex maturity at birth.

Whether or not Negroes are a homogeneous group, irrespective of skin color differences, cannot be stated categorically. Skin color does seem to have definite cultural and biological significance. Its functional significance is perhaps less certain. The only clear relationship of a functional nature indicated by this group is that existing between skin color group of mother and birth weight of infant. Here the associations between socioeconomic status and skin color, and socioeconomic status and birth weight must be borne in mind. The relationship between socioeconomic status and birth weight for this study population is discussed by Crump and his associates.[20]

It is conceivable that any functional significance which skin color may have is closely related to the social significance which skin color has among Negroes; i.e., light color is generally associated with high socioeconomic status, and high socioeconomic status is in turn associated with such factors as heavier average birth weights and longer gestation periods.

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THE PREVENTION OF BILIRUBIN ENCEPHALOPATHY

WILLIAM J. WATERS, M.D.
SYRACUSE, N. Y.

THE treatment of hemolytic disease of the newborn is concerned with the reduction of infant mortality and the prevention of bilirubin encephalopathy.[1] The latter has become the focal point in recent years and, as a result, many articles have been written describing criteria for replacement transfusions. Considerable latitude exists and seems to depend in part on the particular discipline of the writers. The present paper is concerned with a review of the authors' experiences in the management of this problem based on the conviction that bilirubin is toxic to the newborn brain.[2-6] Since this toxicity is closely related to the serum bilirubin level, the capacity of the infant to handle bilirubin as reflected by the latter was used as the principal criterion for replacement transfusion. A high cord level with a rise of serum bilirubin toward critical levels (20 mg. per cent)[7] early was interpreted to indicate impaired capacity and thus dictated the need for early replacement transfusion to prevent brain damage. Significantly, in a number of cases, bilirubinemia of this degree did not develop and thus management without transfusion was elected with good clinical results. Maternal titer and/or a positive Coombs' test by themselves were indicative of sensitization in the mother and potential active disease in the newborn, respectively, but, in the absence of obvious clinical disease, were not considered indications for immediate transfusion; nor was prematurity or past history by themselves, although it was recognized that these were additional hazards which mandated careful evaluation and close surveillance of the infant.

MATERIAL

The cases studied were confined to instances of Rh incompatibility with a positive Coombs' test during a 4-year period from January, 1953, to December, 1956, in a 250-bed hospital (Table I). Cases transferred from outside hospitals are not included in this series. During this period there were 10,876 deliveries of which 65 infants were diagnosed as showing evidence of Rh incompatibility, an incidence of one of 152 births. This figure is not dissimilar to the general average of 1 in 200 quoted by Diamond[8a]; the difference may be explained by the referral of sensitized mothers to this hospital which serves as a center to which complicated cases are referred. However, there were only 6 stillborn infants (9.2 per cent) which is considerably lower than that quoted by Allen and Diamond[9] and no ready explanation is available. The remaining 59 were liveborn but 3 died within a few hours of birth, one

TABLE I

(JANUARY, 1953 - DECEMBER, 1956)

Total deliveries	10,876
Rh incompatibility	65 cases (1-152)
Stillborn	6 cases (9.2%)
Liveborn (Coombs' positive)	59 cases
Mortality	
1. Immediate - no replacement transfusion	3 cases (5.0%)
2. Replacement transfusions	4 cases (6.8%)
a. Brain damage	2 cases (3.4%)

with bilateral polycystic kidneys, the other 2 with severe hydropic disease without a replacement transfusion being attempted.

This report concerns itself mainly with the remaining 56 infants who were liveborn. Since the philosophy of management varied somewhat in these cases, it is necessary to further subdivide them into two groups to evaluate them properly from the points to be established. Thirty-one were supervised by the author using the criteria as outlined previously. The remaining 25 cases were supervised by other staff members who tended to use the more liberal accepted criteria in the literature.

The relationship between maternal titer and management in each of the above groups is shown in Table II. Titers were recorded in all but 1 case. It is seen that there is considerable variation between height of titer and management. In the author's group, where titer alone was not used as a criterion, 7 of the 11 with titers of 1-16, or greater, were managed without transfusion, while in the other groups only 1 in this range was treated in this manner. Disregarding titer alone, it was possible to manage 11 (35.5 per cent) without transfusion which compares favorably with 36 per cent quoted by Walker and Neligan[10] in a much larger series of 264 cases. In the other group, where it would appear more emphasis was placed on maternal titer, only 4 (16 per cent) were treated without transfusion. All of the infants so treated in both groups are free of sequelae after follow-up at the present time.

TABLE II. MATERNAL TITER IN RELATION TO MANAGEMENT IN EACH SERIES

	TITERS	1-1	1-2	1-4	1-8	1-16	1-32	1-64	1-256
Author	Conservative			4		2		5	
	Exchange	1		1		6	1	5	4
Other	Conservative	1		1		1			
	Exchange	2		3		5	1	8	4

The pertinent clinical details of the infants managed without transfusion are illustrated in Table III. It will be observed that in 8 cases there was no detectable jaundice during the hospital course and in the remaining 7 the earliest onset was at 12 hours of age with the majority at or after 24 hours of age. In addition, there was almost a complete absence of other signs of clinical disease in these cases. Of interest also is the variation in hemoglobin values at birth which ranged between 13.0 Gm. per 100 c.c. and 19.5 Gm. per 100 c.c.

TABLE III. CONSERVATIVE CASES

CASES	BIRTH WEIGHT	CLINICAL JAUNDICE	ONSET (HR.)	SERUM BILIRUBIN LEVELS			TITER	PREGNANCY	Hgb. AT BIRTH GRAM %	CLINICAL DISEASE
				CORD MG. %	PEAK RECORDED MG. %	AGE AT PEAK (HR.)				
1	7^{10}	None	--	--	6.2	24	1-16	VI	15.5	None
2	7^{9}	None	--	0.4	0.8	24	1-64	III	15.0	None
3	7^{8}	Present	24	1.9	10.0	48	1-64	IV	13.0	None
4	9^{5}	None	--	--	--	--	1-64*	I	--	None
5	7^{13}	Present	<24	3.9	15.8	72	1-64	III	14.0	None
6	5^{8}	Present	18	2.3	12.2	72	1-4	V	19.3	Liver and spleen 2 F ↓†
7	6^{11}	None	--	1.4	3.2	24	1-4	III	16.0	None
8	9^{4}	Present	72‡	2.3	9.5	50	1-64	V	16.0	Liver 2 F ↓
9	7^{4}	Present	24	1.6	5.0	48	1-4	VI	14.5	None
10	6^{13}	None	--	1.4	2.2	16	--	III	15.0	None
11	7^{10}	None	--	--	5.0	72	1-64	IV	13.5	Liver and spleen 1 F ↓†
12	8^{14}	None	--	1.1	3.8	48	1-16	IV	15.8	None
13	7^{2}	None	--	1.5	4.1	15	1-16	IV	14.5	None
14	6^{15}	Present	12	--	11.9	28	1-1	V	18.8	Liver and spleen 1 F ↓†
15	5^{10}	Present	72‡	2.2	8.2	50	1-4	III	16.0	None

*Three previous transfusions Rh positive blood. (?)
†Fingerbreadths palpable below costal margin.
‡Clinical observation in chart.

In the combined replacement groups, there were 4 deaths (7.1 per cent) all in severely diseased infants which compares favorably with 6 per cent quoted by Walker and Neligan.[10] Two of these died at 48 hours of age and, at post-mortem examination, extensive pulmonary hemorrhage was found in addition to severe erythroblastosis fetalis. One died at 24 hours of age and showed generalized edema in addition to severe erythroblastosis fetalis. Although none of the above 3 infants showed straining of the brain, the fourth one demonstrated this at post-mortem examination.

The clinical and laboratory details of the last case deserve additional comment and are further illustrated in Fig. 1. This mother had been followed through two previous pregnancies with elevated titer (1-64) and, although the Coombs' test was positive in each instance, the infants were managed successfully without transfusion since at birth there were no significant signs of clinical disease and bilirubinemia of sufficient degree did not develop early. In this fifth pregnancy, the titer rose to 1-256 and, at birth, marked signs of disease were present, including pallor, hepatosplenomegaly, and ecchymoses. The initial replacement transfusion was done at 2 hours of age and yet the serum bilirubin continued to rise despite three subsequent transfusions. The significance of this rise is more readily appreciated when the hemoglobin value obtained at birth is noted (6.7 Gm. per 100 c.c.). Using the arbitrary value of 17.6 Gm. per 100 c.c. as a normal value[8b] and disregarding new blood formation, the minimum destroyed hemoglobin would be 17.6-6.7 or 10.9 Gm. per 100 c.c. Accepting 300 c.c. as the total blood volume, the minimum amount of destroyed hemoglobin would be three times 10.9 Gm. or 32.7 Gm. The latter must have taken place in

utero and was deposited in the fetal tissues. Thus, a large reservoir existed which served as the source of bilirubin even though early and repeated replacements had been accomplished. Watson[11] states that potentially 34.7 mg. of bilirubin may be derived from 1 Gm. of hemoglobin. In this instance then more than 1 Gm. of bilirubin may have been presented to the infant for clearance which he was incapable of doing before brain damage occurred. therefore, contributed further to the high serum levels of indirect bilirubin and the complication of brain damage.

The second case of brain damage did not occur in the author's group and probably resulted in part from laboratory error in the bilirubin determination and thus might have been prevented. Accuracy in this procedure is obviously of the utmost importance to the clinician charged with the responsibility of these cases. Correlation

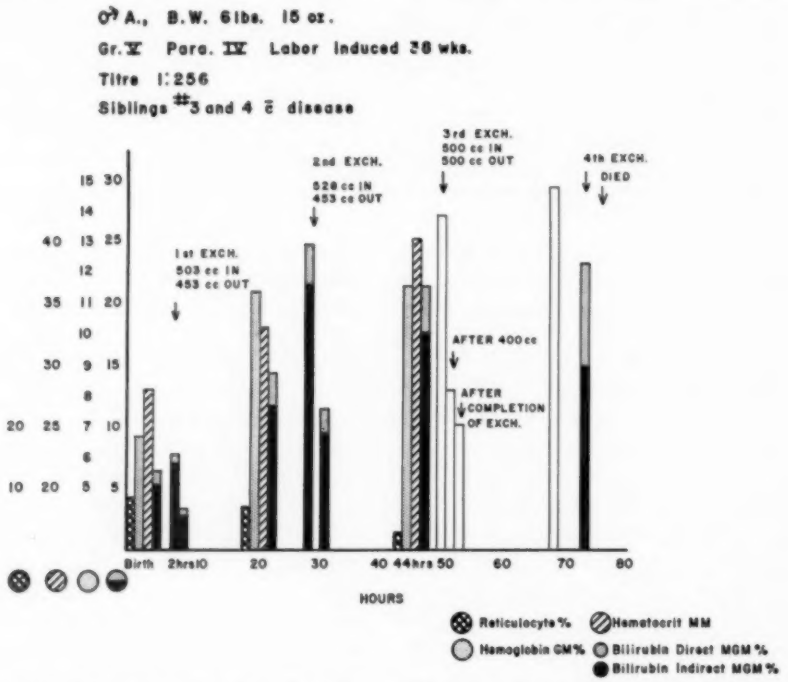

Fig. 1.—Hematological data as illustrated except open bars at 50 and 70 hours represent total bilirubin mg. % without the separate fractions being determined at these intervals.

The exchange transfusions accomplished the removal of only a small fraction of this amount[12] and, thus, the majority was left to be conjugated by the liver. The impairment of glucuronide production and conjugation noted in newborn infants,[13] with the clinical appearance of the jaundice may be difficult and in any event must be based on clinical judgment. However, this case re-emphasizes further the significance of scrutinizing laboratory reports in relation to clinical appearance in order to

evaluate them properly. Whenever there is disagreement, immediate recheck is essential.

Re-exchanges were done primarily when the serum bilirubin continued to rise toward critical levels (20 mg. per cent) and the time for peak levels had not passed, namely, usually after 3 days in the full term and not until the fourth to sixth day in premature infants.

DISCUSSION

Although reduction in infant mortality is to be desired, a significant percentage of infants with hemolytic disease of the newborn due to Rh incompatibility will be either stillborn or hydropic and severely ill at birth. These are usually not salvageable with current management and pose a problem for further investigation and improvement.

At the present time, therapy is primarily effective in preventing bilirubin encephalopathy in those infants who develop jaundice early and, subsequently, if left untreated, may develop this serious complication of brain damage.

The course of management followed by the author in the previously described cases was established following the identification of the pigment within the cytoplasm of the brain cell as bilirubin.[2, 3] In this connection, it is important to re-emphasize that although in those investigations other heme pigments were identified in the peripheral blood,[2] bilirubin was the only pigment demonstrable in the brain cells. Subsequent studies strengthened the conviction of bilirubin toxicity. Staining of the brain was produced in newborn rats by the injection of a bilirubin solution indicating significant biochemical and physiologic differences in this age period.[4] The latter were in part highlighted by the demonstration in vitro of a striking reduction in oxygen uptake in newborn rat brain hemogenates as compared with adult brain homogenates[5] and the localization of inhibition at the level of the pyridine nucleotides.[6]

Most recently, glucuronic acid production in newborn and premature infants was demonstrated as variable and less than in adults and conjugation in the immediate newborn period impaired. Therefore, the serum bilirubin level reflects best the potentiality of any given infant for brain damage. Admittedly better measurements are needed for assessment of the latter and continued investigation into this aspect of the problem is needed.

It should also be borne in mind that other factors may be additive in terms of toxicity. Crosse and Meyer[14] and Allison[15] have suggested that vitamin K in large doses leads to an increased incidence of brain damage in premature infants and Silverman and associates[16] reported an increased incidence in prematures with routine prophylaxis using Gantrisin and penicillin. In the light of recent studies we may speculate that these and other, as yet unidentified, substances may be additive by various mechanisms in terms of toxicity at the cellular level in the newborn infant.

Those infants who are clinically free of disease and have only a positive Coombs' test at birth, regardless of maternal titer, should be watched closely for signs of jaundice; if this occurs early, particularly within the first 12 hours of life, replacement transfusion is indicated. In this con-

nection it should be re-emphasized also that the development of bilirubin encephalopathy is usually between the third and fifth day of life[17] which corresponds with the peak serum bilirubin levels. The earliest recorded occurrence is at 18 hours of age[18] and, therefore, in general there is time for careful evaluation in an otherwise well infant.

Those infants with obvious clinical signs of disease at birth should be subjected to replacement transfusion promptly, but it should be recognized that the presence of edema carries a very poor prognosis for survival.

However, it is our observation, as well as others, that a significant number of infants who do not fall into the above classifications will do well without a replacement transfusion and thus need not be subjected to the hazards of this procedure which include sepsis, trauma, and thrombocytopenia. The latter may be magnified in unskilled hands.

In those cases requiring intervention, the incidence of brain damage should be extremely low. In rare cases, the load of bilirubin may be so great that present-day techniques are not sufficient to prevent encephalopathy.

SUMMARY

1. Maternal titer values and/or a positive Coombs' test by themselves are not an indication for replacement transfusion in hemolytic disease of the newborn due to Rh incompatibility. The main emphasis should be placed on the clinical condition and early course of the newborn infant, particularly the ability to handle bilirubin.

2. A demonstrated rise of serum bilirubin toward critical levels (20 mg. per cent) early, particularly within 12 hours, remains the best single criterion for the need of replacement transfusion in questionable cases. Close supervision is essential.

3. Clinical judgment, which requires a thorough understanding of the clinical and laboratory data, may indicate the necessity of transfusion in individual cases. Therefore, it is desirable to refer these infants to a Center if adequate facilities and personnel are not available. The procedure itself is not without hazard, particularly in the hands of unskilled personnel.

4. Replacement transfusions by present methods may be inadequate, in rare instances, to control the serum bilirubin level and prevent brain damage.

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A Danger of Vaccination

June 27, 1857.—Dr. Buck reported two cases of *Erysipelas following Vaccination*. They were novel to him, and might be interesting to the Society.

In March last, he vaccinated a child a few weeks old, and at the end of a week a good vesicle had formed; there was no areola. He charged some quills, and supposed that everything would go on according to the rule. The third day after this, the child was attacked with erysipelas about the pustule, which soon involved the whole arm, and extended to the chest, running its course very rapidly. Death ensued on the eighth day from the time when the disease was first seen. He vaccinated several children with matter taken from this child, and they all did well.

On the 4th of the present month, he vaccinated a healthy child, also a few weeks old, and on the seventh day charged his quills. Nine days after this, the sixteenth day after the vaccination, erysipelas appeared on the arm, ran down the chest, abdomen and the legs; this patient is now recovering. He also vaccinated several children with lymph taken from this case, and no trouble had as yet ensued.

There was no case of erysipelas in the houses where either of these children were living, and no predisposition to this disease, as far as he knew, in either of the families to which they belonged. These are the only cases of the kind Dr. Buck has ever met with.

Extract from the RECORDS OF THE SUFFOLK DISTRICT MEDICAL SOCIETY, THE BOSTON MEDICAL AND SURGICAL JOURNAL, Feb 4, 1858.

THUMB- AND FINGER-SUCKING: A STUDY OF 2,650 INFANTS AND CHILDREN

ALFRED S. TRAISMAN, M.D.,* AND HOWARD S. TRAISMAN, M.D.
CHICAGO, ILL.

MUCH has been written on the various phases of finger- and thumb-sucking by pediatricians, psychiatrists, psychologists, dentists, and orthodontists. Even lay publications have devoted much space to this debatable subject. However, few statistical studies have been made of this habit in healthy infants and children.

Roberts[1] investigated 30 infants between 7 and 8 months of age; 15 sucked their thumbs, and 15 did not suck their thumbs. She obtained information pertaining to the type of feeding; number of feedings per day; changes in feeding schedule; time per feeding; and onset of thumb-sucking. The majority began to suck their thumbs during the first 3 months of life. None of these infants used a pacifier. It was concluded that non-thumb-suckers spent a longer time per feeding than those babies who sucked their thumbs. This is in agreement with Levy's[2-4] observations that the amount of time spent in sucking is the primary determinant of the finger- or thumb-sucking habit.

Brazelton[5] evaluated 70 healthy infants regarding the occurrence of extranutritional sucking. Sixty-one exhibited an appreciable amount of sucking, which was satisfying to the infant. Onset was from birth to 3 months of age, with increasing intensity to 7 months of age. At this time thumb-sucking began to decrease. Only 4 infants continued to suck their hands at 1 year of age. Past 2 years of age, only 2 infants continued this habit. He stresses "the importance of extranutritional sucking as a source of gratification in infancy. Its occurrence is normal and its disappearance is spontaneous in most infants when not inhibited." This latter statement is in agreement with what has been previously written.[6, 7]

Klackenberg[8] reported his experiences with 259 children between 4 and 6 years of age. Of this group, 50 per cent had been thumb-suckers. At 1 year of age, 50 per cent of the 129 infants who sucked their thumbs persisted with this habit; 47 per cent were sucking their thumbs at 2 years of age. The percentage of those who persisted with this habit gradually decreased over the years, until only 21 per cent of the 129 children sucked their thumbs at 6 years of age. In 100 cases he established the onset of the habit as follows: prior to 3 months of age, 54 per cent; 3 to 5 months of age, 22 per cent; 6 to 9 months of age, 14 per cent; after 9 months, 10 per cent. There was no significant difference in the incidence of thumb-sucking among breast-fed infants. He found an equal

*6354 North Broadway, Chicago 40, Ill.

number of children who sucked and did not suck their thumbs among those who were fed for 20 minutes as well as those who were fed for shorter periods.

METHOD OF STUDY

It was the purpose of this study to investigate finger- and thumb-sucking and specific factors that we thought were pertinent to this habit. When we use the term "thumb-sucking" it will mean "finger- or thumb-sucking." Thumb-sucking as discussed in this paper refers to placing the thumb or fingers deep into the mouth many times every day and night and exerting definite sucking pressure. A total of 2,650 infants and children were selected in consecutive order from a general pediatric practice. All patients were Caucasian and came from the middle socioeconomic group of our population. None of these infants or children had any chronic or congenital diseases that could alter their feeding habits. They ranged in age from birth through 16 years.

The mother of each patient was questioned verbally, by use of open-end questions, regarding feeding habits, whether the baby sucked his thumb or not, the age of onset and termination of this habit, length of time of feedings, and other factors that will be discussed later. We urged each mother to keep a record of length of time of feedings. We checked these items in our infants during monthly visits the first year of life, quarterly visits the second year of life, and semiannual visits thereafter. All patients were followed from birth, and the parents were questioned in the same way regarding this habit, beginning with the infant's first visit to us. One of us (A. S. T.) followed many of these patients until they were 17 years of age. The parents were not told they were being included in a study of thumb-sucking. Parents who could not be specific in their answers or remember certain items were not included in this study. We did not ask the questions in a leading manner or solicit answers. Every effort was made to be as objective as possible.

All infants were on a demand feeding schedule and averaged six feedings per day for the first 3 months of life. A few infants took 5 or 8 feedings per day during this period.

In the older children, special attention was given to the examination of the mouth, the incidence of malocclusion, and whether or not the patient was receiving orthodontic care.

RESULTS OF STUDY

1. A total of 2,650 patients was studied; 1,340 were male, and 1,310 female.

2. There were 1,208 thumb-suckers, 45.6 per cent of the total group. Of these, 596 were male and 612 female. Since the sex distribution is not statistically significant, further breakdown of groups according to sex will be omitted. Seventy-five per cent of the infants who sucked their thumbs began to do so during the first 3 months of life, and the other 25 per cent during the remainder of the first year of life. We frequently noticed thumb-sucking in the newborn nursery and during the neonatal period.

3. Three hundred infants (11.3 per cent of total group) were partially or completely breast fed. Average duration of this type of feeding was 4.4 months. Of this number, 130 (43.3

per cent) sucked their thumbs. Breast feeding was not found to be a significant factor in the incidence of thumb-sucking.

4. The majority of our patients took less than 30 minutes to feed. Of the patients in the "fast" and "average" group, 41.7 to 45.8 per cent were thumb-suckers (Table I). This is probably significant. The higher incidence of thumb-sucking, 62.7 per cent, in the "slow" group will be discussed later.

TABLE I

FEEDING TIME (MINUTES)	NO. IN GROUP	PER CENT OF TOTAL GROUP	THUMB-SUCKERS	
			NO.	PER CENT
10 or less ("fast")	524	19.7	240	45.8
15-25 ("average")	1,639	61.9	683	41.7
30-60 ("slow")	419	15.8	263	62.7
60 or longer	68	2.6	22	32.3

5. The average age at which all thumb-sucking stopped was 3.8 years. A few stopped during infancy, and some as late as 12 to 15 years of age. Most parents expressed minor concern about this habit during the first 2 to 3 years of age. As the habit persisted past 3 years of age, their anxiety increased.

6. Pacifiers were not recommended. Of 28 patients who used them, 8 sucked their thumbs.

7. Malocclusion was diagnosed by us if there was a protrusion of the anterior upper teeth with a normal molar relationship, or if there was a protrusion of the maxilla with an abnormal molar relationship of the first maxillary molar being one-half tooth forward from the normal position. Patients were then referred for orthodontic care. If the orthodontist concurred in our findings, the patient was classified as having malocclusion. Malocclusion occurred in 211 patients, or 7.9 per cent of the total group. Of these children, 117, or 55.4 per cent, sucked their thumbs. Of 86 children who wore braces for malocclusion, 53 had never engaged in the sucking habit and 33 sucked their thumbs. This is not statistically significant. Of thumb-suckers, 9.7 per cent developed malocclusion, compared to 6.5 per cent of the nonthumb-suckers. There is a highly significant difference between these two percentages, pointing to a definite effect of thumb-sucking on malocclusion. The degree of relationship between thumb-sucking and malocclusion, though statistically significant, is obviously very small and of limited extent. However, there is clearly some relationship. One reason for this may be that thumb-sucking beyond a critical age only will result in malocclusion. This is a theoretical possibility, but it is being studied. It is interesting to note that 4 children had mechanical devices placed on their molars to break the sucking habit. This was successful with 1 child and failed with 3 children. More psychological distress was observed in these latter children after insertion of the dental bar than was seen during the thumb-sucking period.

8. Psychological problems in the children were diagnosed as such if there was an inadequate adjustment to their environment. This was evaluated with respect to school and learning difficulties as reported to parents by the teachers; poor peer relationship as noted by parents and/or friends; enuresis without organic pathology; night terrors; excessive sexual interest as manifested by masturbation; and food fads producing obesity or poor nutrition. Psychological problems occurred in 137 patients, or 5.2 per cent of the total group. Of these 137 patients 67 (49 per cent) sucked their thumbs. There was no statistical relation between psychological problems and thumb-sucking.

9. Two hundred and eighty-two infants, 10.6 per cent of total group, had colic. One hundred and twenty-nine of these babies, 45.7 per cent, sucked their thumbs. There was no relationship between colic and thumb-sucking.

10. Of the 1,208 patients who sucked their thumbs, 976, or 80.8 per cent, still persisted with this habit at 2 years of age. Only 48 infants, 3.9 per cent of those who sucked their thumbs, stopped this habit prior to, or at, 1 year of age. There are 96 infants 1 year of age at the time of writing who are still sucking their thumbs.

11. We were unable to find any significant difference in the thumb-sucking habit between only children and those with 1 to 4 siblings (Table II). Three hundred and forty-two children were omitted from this part of the study because of lack of follow-up of the patient and/or siblings. There was also no significant correlation of this habit among identical and fraternal twins, and between twins and one or more siblings. One cannot say that identical and fraternal twins will have similar thumb-sucking habits.

DISCUSSION

To our knowledge, this is the largest series of patients reported that has been statistically analyzed. Of our 2,650 infants and children, 45.6 per cent sucked their thumbs. There was no sex difference, which is contrary to Gesell and Ilg's[7] observation that more boys than girls suck their thumbs. Breast feeding was not a significant factor in the incidence of thumb-sucking.

Feeding time was probably significant in the incidence of thumb-sucking. The majority of individuals in our study, 81.6 per cent of the total group, took 30 minutes or less to feed. Of patients in the group of "fast" and "average" feeders, 41.7 to 45.8 per cent sucked their thumbs (Table I). Bakwin[6] believes that inadequate sucking time as a cause of thumb-sucking is of minor importance.

TABLE II

	TOTAL	SUCKED THUMB		DID NOT SUCK THUMB	
		NO	%	NO.	%
Total group	2,308	1,037	44.9	1,271	55.1
Siblings	1,447	646	44.6	801	55.4
Nonsiblings	861	391	45.4	470	54.6

Of interest is that there was a significantly higher incidence of thumb-sucking in infants who fed 30 to 60 minutes. Our opinion is similar to Pearson's,[9] namely, that stimulation

of the lips and mouth, which are richly supplied with sensory nerve endings, gives a marked feeling of pleasure. Once this satisfying sensation is experienced, there is a desire to have it repeated. Therefore, the more a baby sucks, the more the oral structures are stimulated, and the more gratification is obtained. On this basis the infant would tend to suck his fingers or thumb because the pleasure he derives has been so implanted and developed. The baby who spends less time for nutritional sucking does not have this pleasure so strongly developed because there is less oral stimulation, and he may not suck his thumb. Sears and Wise[10] showed that the oral drive is strengthened by the longer retention of the sucking method of feeding. Therefore, a substitute sucking habit would increase with a decrease in nutritional sucking. The strength of the oral drive, and not frustration in weaning, would determine the incidence of thumb-sucking.

The smallest percentage of those who sucked their thumbs was in the group that took 60 minutes or longer to feed. We cannot offer a suitable explanation for this.

The average age at which the thumb-sucking habit stopped spontaneously was 3.8 years. This is longer than the 2-year limit that has been mentioned in the literature. However, dentists say that cessation of the habit at this age is compatible with normal tooth and dental arch formation. If malocclusion is caused by the thumb-sucking, the displaced teeth and arch will spontaneously correct themselves after the sucking has ceased, especially after development of permanent dentition.[11-16] Ruttle[16] states that "the effect of thumb and finger habits on the molar occlusion merely approaches statistical significance, and does not attain clinical utility."

Of the 211 patients who had malocclusion, 117 sucked their thumbs (9.7 per cent of all thumb-suckers). Of 86 children who wore braces, only 33 sucked their thumbs. This is not significant. Johnson[17] studied 989 cases of malocclusion and found 173 patients (17.5 per cent) who sucked their thumbs. In 24.5 per cent of the thumb-suckers, the habit persisted one year or less. Sixty per cent had broken the habit by the end of the third year. According to an editorial[18] that most adequately summarized the topic of thumb-sucking, when one considers thumb-sucking as a whole, it is a rare cause of dental deformities. We are in disagreement with those[19-21] who maintain that forceful measures should be instituted to stop this habit because of possible dental malformations and psychological problems.

Dental devices to stop thumb-sucking were not used in enough cases to be truly evaluated. We found that the habit terminated spontaneously in the great majority of patients, and at an early enough age so that routine use of such a bar was not the usual procedure. Indications for the use of a dental bar, and the related problems, are discussed by Graber.[15]

There was no correlation between colic and thumb-sucking.

Twenty-eight patients used a pacifier, of whom 8 sucked their thumbs. This small number cannot be statistically evaluated. However, we have seen patients, who did not suck their thumbs while using a pacifier, begin this habit when the pacifier was discontinued.

Klackenberg[8] observed no thumb-sucking in 28 infants who used a pacifier over 3 months. Starr[22] prefers the pacifier to the thumb, from the orthodontist's standpoint. He believes a child can be more easily separated from the pacifier than from his thumb. Rittelmeyer[23] investigated 364 children to determine the value of the pacifier in the prevention of thumb-sucking; 87 children sucked their thumbs and 54 used pacifiers. Among those who did not use pacifiers, 27 per cent were thumb-suckers. Of the 54 who did use them, only 8 sucked their thumbs. Of these, 5 were thumb-suckers before pacifiers were instituted. In only 3 instances did the pacifier fail to prevent thumb-sucking. Only 14 children in this study stopped the sucking habit by the time they were 2 years of age, and 12 continued it after 7 years of age. However, only one child used a pacifier past the age of 2 years.

No correlation was found between psychological problems and thumb-sucking. Most authorities are of the opinion that the great majority of thumb-sucking stops spontaneously around 2 or 3 years of age and that forceful cessation of the habit will create neurotic symptoms and personality problems which are more serious than the sucking habit.[6, 7] One definitely cannot predict psychological problems because a child has been or is actively engaged in thumb-sucking. Kaplan[24] believes that thumb-sucking that persists after the usual time for disappearance is a symptom of emotional disturbance for which the treatment must be based upon the etiology. Persistence of the habit may be due to boredom, fatigue, or unhappiness.

We are in agreement with others[6, 25, 26, 27] that the problem of thumb-sucking has been overemphasized and parents unduly alarmed. Parents should be informed and reassured about the relative harmlessness of this habit. Occasionally, it may continue because it has been established as a habit even though most of the psychological implications have disappeared.

Our findings differ from that of previous reports[5, 8] that the majority of patients who sucked their thumbs stopped by 1 or 2 years of age. In our study, 80.8 per cent of those who sucked their thumbs persisted at 2 years of age, while 3.9 per cent of those who sucked their thumbs stopped at 1 year of age or earlier. These figures are close to Johnson's[17] results. From our findings it would appear incorrect to tell anxious parents that their child will stop this sucking habit by 1 or 2 years of age.

SUMMARY

A study of finger- and thumb-sucking and related factors in 2,650 infants and children has been statistically analyzed and clinically evaluated. The pertinent literature has been briefly reviewed.

The authors wish to express their thanks to Dr. Thomas Baffes for his analysis of the statistics utilized in this study.

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MONALDI DRAINAGE IN THE MANAGEMENT OF POSTINFECTIOUS PULMONARY CYSTS

JOSEPH RAKOWER, M.D., AND PINKHAS WAYL, M.D.
JERUSALEM, ISRAEL

WITH the striking decrease in pneumococcic infections since the introduction of antibiotic drugs, there has been a relative increase in the incidence of staphylococcic pneumonia.[3, 7] Concurrently, there has been an increase in the incidence of staphylococcic empyema, spontaneous pneumothorax, and postinfectious air cysts. It is estimated that these air cysts (also called pneumatoceles, postinfectious bullae, or blebs, the term depending on size and location within the lung) occur in 25 per cent of the cases of staphylococcic pneumonia.[6] Continuous closed drainage in the treatment of empyema and spontaneous pneumothorax is universally accepted,[1, 2] but opinions differ as to its use in management of postinfectious air cysts. These cysts are usually thought to be due to reversible changes in intrapulmonary tension and tend to disappear after a few weeks or months. However, in some cases they persist indefinitely. The purpose of this paper is to present a case of multiple postinfectious air cysts and to indicate the role of continuous aspiration in their treatment.

CASE REPORT

An acutely ill 10-year-old boy was admitted to the hospital in July, 1954. In 1951, he had developed measles, which was complicated by left-sided otitis media. After recovery, a foul secretion from the left ear persisted.

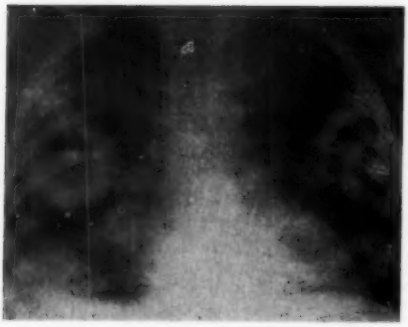
The present illness began in June, 1954, with high fever, rigor, cough, dyspnea, and pains in the chest. Two weeks after the onset of the illness he began to cough and to expectorate foul-smelling sputum. Upon admission he was in poor general condition, dyspneic, cyanotic, and had a fever of 40° C. Examination of the chest revealed bilateral dullness, bronchial breathing, and medium râles in the upper and lower zones. The erythrocyte sedimentation rate was 94 mm. in the first hour (Westergren) and the leukocyte count was 26,000 per cubic millimeter. X-rays of the chest showed four abscesses in the upper and lower lobes of both lungs (Fig. 1).

Staphylococcus aureus was cultured from the sputum and found to be sensitive to chloramphenicol. After treatment with chloramphenicol, the temperature subsided and the general condition improved, although expansion of the abscesses was seen on x-ray films. In August, 1954, the abscess in the left upper lobe suddenly ruptured (Fig. 2), producing a spontaneous pneumothorax. The boy was found unconscious, cyanotic, and was frothing at the mouth. The breathing was irregular and no pulse was found. Continuous intrapleural aspiration was instituted. Rapid improvement followed and after 6 days of continuous suction, roentgenograms showed disappearance of the abscess in the left upper lobe.

Two weeks later a second dramatic spontaneous pneumothorax occurred,

From the Department of Chest Diseases, Rothschild Hadassah University Hospital, Jerusalem, Israel.

Fig. 1.



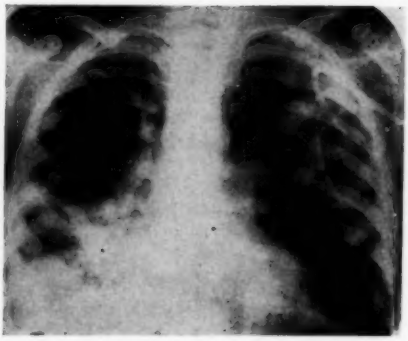


Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 1.—Abscesses in the left upper, left lower, right upper, and right lower lung fields.

Fig. 2.—Spontaneous pneumothorax on the left side, 2 giant tension abscesses on the right side.

Fig. 3.—Second spontaneous pneumothorax on the left. Conversion of the right abscesses into giant air cysts.

Fig. 4.—Healing of the left lung after pleural drainage. Suction drainage of the right lower air cyst.

Fig. 5.—Healing of the right lower air cyst. Suction drainage of the right upper air cyst.

Fig. 6.—Roentgenogram upon discharge shows slight fibrosis at right base.

following rupture of the abscess in the left lower lobe (Fig. 3). Again intrapleural aspiration was instituted and, after 4 days, x-ray films showed that the lung had re-expanded and that the abscess in the left lower lobe had disappeared. However, the two abscesses in the right lung occupied almost the entire volume of the right lung (Fig. 3). Bronchoscopy showed redness of the bronchial mucosa, particularly at the right bronchus. Attempts to deflate the cavities by bronchial suction were ineffective. In November, 1954, the temperature again rose to 40° C. Swelling developed over the left mastoid and a radical mastoidectomy was performed. The tympanic cavity and the paratympanic region were filled with granulomatous tissue. After removal of this tissue, pus under pressure was released. The lateral sinus was found to be thrombosed. The postoperative course was uneventful.

Since the giant cavities in the right lung were still found to be present after 8 months of treatment with various antibiotic drugs, transpleural drainage was decided upon. Pleural puncture revealed that over the right base the pleural cavity was obliterated. In the upper area the pleura was free in the mammary line but obliterated in the posterior axillary line. On Feb. 14, 1955, drainage of the lower cavity was instituted (Fig. 4). The intracavitary pressure was +4, +10 cm. of water. A multieyed catheter was inserted into the cavity and was connected with an electrical suction machine. After one week of continuous suction, the cavity disappeared completely. On Feb. 22, 1955, drainage of the upper cavity was instituted (Fig. 5). Intracavitary pressure was +6, +12 cm. of water. After 3 days of suction, this cavity also disappeared. During suction of both these cavities, a few cubic centimeters of thick, foul pus was removed. From this pus, as well as from that obtained during bronchoscopy and mastoidectomy, *Staphylococcus aureus* and *Bacillus proteus* were cultured.

The boy left the hospital in March, 1955, completely recovered. Radiograms of the chest upon discharge revealed only slight fibrosis at the right base (Fig. 6).

DISCUSSION

The annular shadows appearing during primary staphylococcic pneumonia or hematogeneous staphylococcic bronchopneumonia are actually giant tension abscesses. The radiographic and clinical history of our patient shows clearly the evolution from bronchopneumonic infiltrations to thick-walled, pus-filled cavities. These later swelled to become thin-walled balloons, due to mechanical factors, with infection now playing only a minor role. Similar formation of emphysematous bullae from miliary or cavitary staphylococcic abscesses had demonstrated in rabbits following intravenous injection of *Staphylococcus aureus*.[5] The giant air cysts constitute a special form of bullous obstructive emphysema resulting from check-valve obstruction produced by bronchial exudate and edema and later by cicatricial bronchiolar stenotic fibrosis. If they persist indefinitely they are frequently mistaken in later years for congenital cysts.

There are no reports dealing primarily with the treatment of these postinfectious cysts. There is, however, an extensive literature on the treatment of emphysematous bullae which appear mostly in cases of asthma or chronic obstructive emphysema. Head and Avery[4] successfully treated 8 patients with emphysematous bullae by Monaldi intracavitary drainage. This type of drainage has been successfully employed in the treatment of lung abscess since 1940.[10] Up to the present time, 127 cases, of which 116

recovered, have been recorded.[8] Since postinfectious air cysts are actually giant tension abscesses, Monaldi drainage is also indicated in their treatment. Expectant treatment should not exceed a period of 6 months. On the other hand, intervention may be indicated much earlier if there is marked displacement of the mediastinum or appearance of dyspnea.

The solitary giant cyst or multiple cysts located in different lobes are the only type of cysts for which Monaldi drainage is indicated. There should be a pleural bridge of adhesions at the point of intervention. Since the primary foci of suppuration are usually located peripherally, pleural reaction with subsequent obliteration of the pleural cavity is frequently present. In the absence of pleural adhesions, obliteration of pleura by poudrage is indicated.

When more than one cyst is present in a single pulmonary unit, but sufficient normal lung tissue remains, excision of the walls of the cysts and suture of the parenchyma according to the procedure of Naclerio and Langer[9] is indicated. When the postinfectious cysts have destroyed a segment or a lobe, resection of the pulmonary unit is the procedure of choice.

SUMMARY

A 10-year-old boy developed 4 hematogenous staphylococcic pulmonary abscesses following otitis media complicated by mastoiditis and thrombophlebitis of the lateral sinus. Two of the abscesses perforated and the pneumothoraces as well as the perforated abscesses were cured by continuous closed pleural drainage. The other 2 abscesses progressively inflated and were converted into giant cysts, which persisted despite 8 months of antimicrobial treatment. They healed after a few days of intracavitary aspiration. The various methods of treatment of postinfectious air cysts are discussed.

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ACCIDENTAL DIGITOXIN POISONING IN CHILDREN

Report of a Case and Review of the Literature

Curtis C. Drevets, M.D.
Iowa City, Iowa

INTRODUCTION

ACCIDENTAL drug poisoning in children is common and is being seen more frequently each year. Digitalis intoxication is common also and is increasing, paralleling the increasing number of older people and hence the number of patients requiring treatment with digitalis. Accidental digitalis poisoning is rare, especially in children, as evidenced by the scarcity of material in the literature on this subject. However, small children have an unquenchable curiosity, which causes them particularly to put things in their mouths. It is thus a grave danger for older people to leave digitalis within the reach of small children in the house.

Bergy and associates[1] reported a case of overwhelming acute digitoxin poisoning in an adult. They surveyed the world literature and found seven other cases of accidental digitalis poisoning. However, none of these was a child. A further search of the English medical literature revealed two case reports of accidental digitalis poisoning in children. Both of these cases occurred in the British Isles.

Allen[2] reported a case of a 3-year-old child who swallowed 1.2 mg. of Digitaline Nativelle. After six hours the child began to vomit. On the second day after the ingestion he had a pulse rate as low as 52 per minute. He was treated with atropine and strychnine and on the fourth day apparently had recovered completely.

The second case was reported by Soderberg.[3] The patient was a 2-year-old child who swallowed 33 tablets of folium digitalis (0.05 Gm. each) totaling 1.65 Gm. Gastric lavage was unsuccessful but the child began to vomit in three hours. On the following day, the electrocardiogram showed first degree A-V block (P-R interval, 0.24-0.26 seconds) and a temporary complete A-V block with a varying rate of about 80 per minute. The patient was well clinically on the third day but the electrocardiogram did not return to normal until one month after ingestion of the digitalis.

Recently I observed accidental digitoxin poisoning in a child. In view of its rarity, it was thought to be of considerable interest and worth reporting.

CASE REPORT

A 2-year-old white boy (W. C. G. H. Case #73279) was first seen in the emergency room at 1:00 P.M. on Dec. 20, 1956. Apparently the child had been in his usual good health until noon on the day of admission, at which

time he began to retch and vomit. He became seriously ill quite rapidly and vomited many times. It was not until shortly before admission that the grandmother's bottle of digitoxin was found empty. The family thought the child had taken from 12 to 15 tablets of digitoxin (0.1 mg. size). The child apparently took the digitoxin shortly after 8:00 A.M. on the day of admission. When examined in the emergency room, he was lethargic, vomited repeatedly, and appeared acutely ill. The heart rate was 96 and the rhythm was somewhat irregular. A Grade 2 systolic murmur was heard in the second and third intercostal spaces on the left. The remainder of the physical findings were normal. The child weighed 30 pounds.

Laboratory studies showed the following: hemoglobin, 13.9 Gm.; red blood count, 5.1 million; white blood count, 11,250, 85 per cent neutrophils, 12 per cent lymphocytes, 3 per cent monocytes. Urinalysis showed specific gravity, 1.020; acetone, strongly positive; occasional hyaline cast.

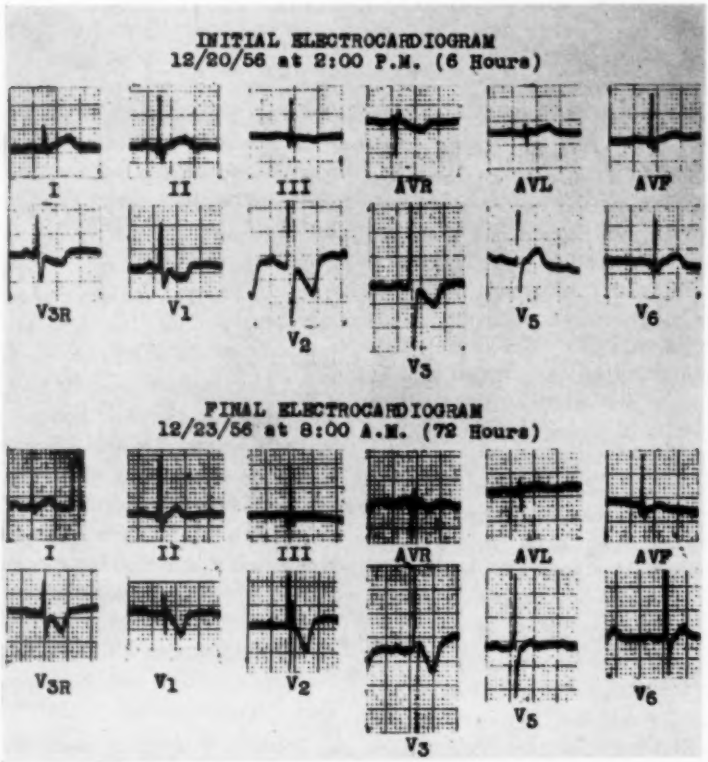

Fig. 1.—The initial and final electrocardiograms are shown here for comparison.

After a gastric lavage, the patient was admitted to the pediatric ward where the initial electrocardiogram was taken (Fig. 1). An attempt to give potassium chloride was unsuccessful because the child was vomiting and was unable to retain oral fluids or medication. He continued to be lethargic and irritable and the pulse revealed "dropped beats." After an electrocardiogram was taken at 7:00 P.M., intravenous fluids consisting of 500 c.c.

of 5 per cent dextrose in water with 10 mEq (750 mg.) of potassium chloride were started at 20 drops per minute. In 3 hours the pulse was less irregular. Occasional twitching of the skeletal muscles was noted about midnight. Repeated attempts to sip water were followed by emesis. At 10:00 A.M. the next day the initial intravenous therapy was followed by 250 c.c. of 2.5 per cent dextrose in half-strength lactated Ringer's solution (39 mg. of potassium chloride). He was still lethargic but responded when aroused. Because of vomiting, an injection of Thorazine (5 mg.) was given at 3 P.M. and another at 8:30 P.M. (Dec. 21, 1956) with fair results. The patient

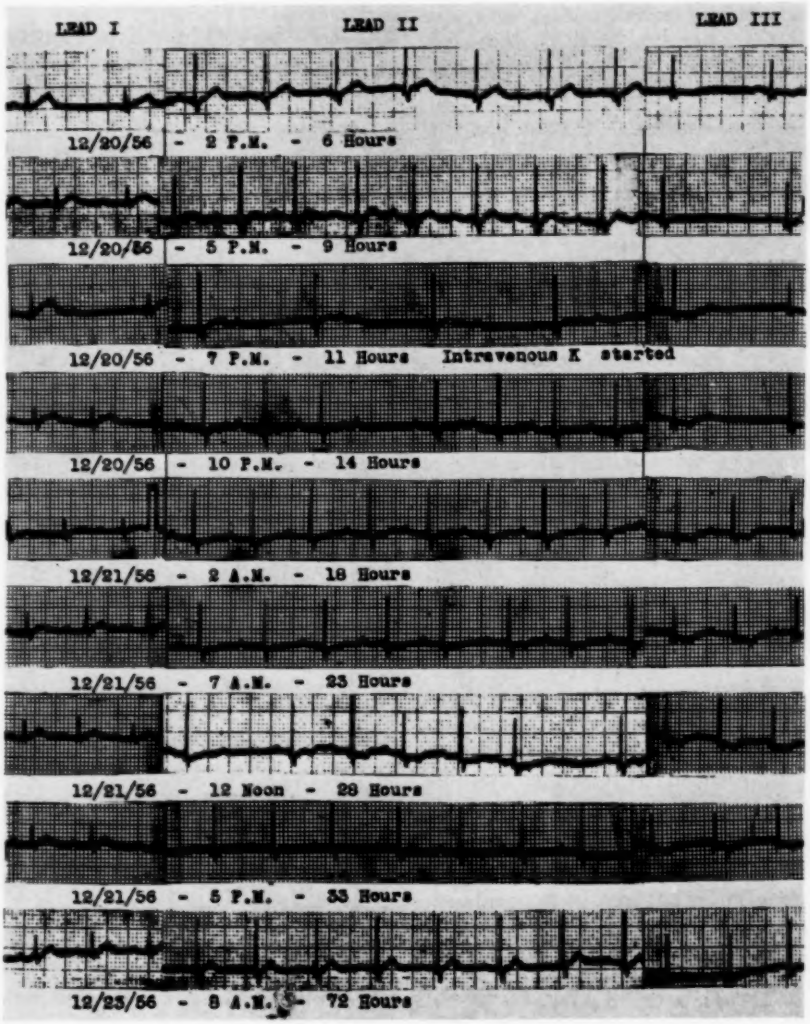
LEAD I
LEAD II
LEAD III
12/20/56 - 2 P.M. - 6 Hours
12/20/56 - 5 P.M. - 9 Hours
12/20/56 - 7 P.M. - 11 Hours Intravenous K started
12/20/56 - 10 P.M. - 14 Hours
12/21/56 - 2 A.M. - 18 Hours
12/21/56 - 7 A.M. - 23 Hours
12/21/56 - 12 Noon - 28 Hours
12/21/56 - 5 P.M. - 33 Hours
12/23/56 - 8 A.M. - 72 Hours

Fig. 2.—Serial electrocardiograms on patient.

was now voiding well and the intravenous infusion was continued with 250 c.c. of 5 per cent dextrose in 0.45 per cent saline. During the evening of the second hospital day, he became much more alert but did not retain oral fluids well until late that evening. He was then given oral potassium chloride, 125 mg. every 4 hours. Two days later the child was alert, eating and drinking satisfactorily, and appeared well. No residual signs or symptoms were noted. The child was dismissed. One week later the patient's physician reported that there were no further symptoms or findings.

TABLE I. DATA FROM SERIAL ELECTROCARDIOGRAMS ON PATIENT (FIG. 2)

HOURS AFTER INGESTION	P-R* INTERVAL (SEC.)	Q-T† INTERVAL (SEC.)	ATRIAL RATE	VENT. RATE	COMMENT
6	0.14	0.28	88	88	Normal sinus rhythm
9	0.23	0.24	107	107	First degree A-V block, rare dropped beat
11	0.18–0.23	0.28	107	54	Second degree A-V block
14	0.25	0.24	103	90	First degree A-V block, occasional dropped beat
18	0.24	0.24	107	107	First degree A-V block
23	0.24	0.24	103	103	First degree A-V block
28	0.19	0.24	109	90	First degree A-V block, occasional dropped beat
33	0.18	0.24	100	100	First degree A-V block
72	0.16	0.24	100	100	Normal sinus rhythm

*Upper limits of normal for 2-year-old child at rate of 90-110 is 0.16 second.
†Lower limits of normal for 2-year-old child at rate of 88 is 0.28 second; at 100 is 0.27 second; at 109 is 0.26 second.

DISCUSSION

In the otherwise healthy laboratory animal,[4, 5] the first toxic manifestations of digitalis poisoning are strong vagal stimulation. They consist of bradycardia, cardiac irregularities, diastolic pauses, and an idioventricular rhythm. This may or may not be followed by increasing muscular irritability resulting in an increase in the ventricular rate, the ventricles functioning independently of the atria. As the toxicity increases, the heart progresses into ventricular fibrillation and death follows. In animals so poisoned, microscopic examination of the heart shows focal areas of necrosis, especially in the subendocardium and in the posterior papillary muscles of the left ventricle. These lesions are more common in older animals and in the presence of experimentally induced hyperthyroidism.

Although digitalis poisoning in man may be manifested by the same variety of rhythmic disorders seen in animals, similar pathologic lesions have not been demonstrated. It is well known that digitalis has been responsible for almost every known type of arrhythmia and conduction disorder.[4, 6, 7]

The symptoms of digitalis intoxication usually begin with anorexia, nausea, and vomiting.[4, 6, 7, 8, 9, 10] Occasionally there may be diarrhea, salivation, abdominal discomfort, substernal pain, and rarely a hemorrhagic gastritis. Respirations may be normal or the patient may become dyspneic. Many patients suffer fatigue and become drowsy. A few lose consciousness. Others become restless, irritable, disoriented, and rarely they may have hallucinations and delirium. Some develop headaches, tremors, myalgias,

arthralgias, and sometimes convulsions. Although it is rare, psychoses may be observed as a late effect. Disturbances in color vision are common and often these patients are unable to focus their eyes properly; others may have diplopia, amblyopia, and scotomata. Occasionally, there are vestibular disturbances and impairment of renal function.

The electrocardiogram[4, 6, 7] first shows flattening of the T wave which later becomes inverted. The usual digitalis ST segment is noted. As toxicity increases, the P-R interval is prolonged and the Q-T interval is diminished. The electrocardiogram shows changes in rhythm and conduction as described.

The patient under discussion demonstrated many of these signs and symptoms. Many of the subjective symptoms may have been missed because of his age. The serial electrocardiograms (Fig. 2) demonstrate well the progression of the toxic effects to one of the most common of the conduction defects.

The toxic dose of digitoxin is difficult to estimate because of the many variables and individual differences. Master[11] states that the initial therapeutic digitalization dose is about 50 to 60 per cent of the toxic dose. Nadas,[12] in a study of the use of digitoxin in 41 children with various cardiac diseases, noted that none of the patients showed a satisfactory response with less than the "average" adult digitalizing dose of 0.01 mg. per pound of body weight. There were also no satisfactory responses in patients requiring more than 0.03 mg. per pound. The majority of their patients showing digitoxin toxicity received dosages of 0.015 mg. per pound of body weight. Considering further that children, in general, require 50 per cent more digitoxin per unit of body weight than adults,[12-14] we would calculate the average digitalizing dose as 0.015 mg. per pound of body weight (using 0.01 mg. per pound as average for adults). Using Master's figures, the average toxic dose for children would be 0.025 to 0.03 mg. per pound of body weight. If we apply these figures to our patient, whose weight was 30 pounds, the estimated toxic dose of digitoxin would be 0.75 to 0.90 mg. The patient received 1.2 to 1.5 mg. of digitoxin, which is well in excess of this estimated toxic dose.

The present treatment[4, 6] of digitalis poisoning is chiefly supportive and symptomatic. Cessation of intake of the drug and promotion of its excretion are desirable. Pronestyl[4, 6, 15] and quinidine[4, 6, 16] have been used to counteract and reverse the arrhythmias. However, the danger of the use of digitalis and quinidine simultaneously has been pointed out by Gold.[16] It would be more desirable to have an agent to use before the onset of the arrhythmia. Numerous workers[17, 18] have used a 10 per cent solution of magnesium sulfate intravenously to correct the arrhythmias induced by digitalis. The disadvantages of the use of magnesium sulfate are its transient action and the occasional tendency to increase the basic arrhythmia.[4] There have been several investigations[4, 6, 19, 20] concerning the use of potassium in digitalis intoxication. Numerous workers have abolished various arrhythmias with potassium; about half succeeded when the arrhythmias were not due to digitalis and almost all succeeded when they were due to digitalis.

It has been demonstrated that there is a depletion of potassium in the myocardium in digitalis intoxication. Also, myocardial potassium depletion is observed in states of anoxia, myocardial failure, myocardial infarction, following diuresis, diabetic acidosis, metabolic alkalosis, and intestinal disorders.[20-24] In these conditions there is increased sensitivity to digitalis. In the isolated heart preparation the effect of digitalis can be enhanced or inhibited by appropriate variation of the potassium ion concentration in the perfusate.[25] It has been suggested that potassium might inhibit the cardiac effects of digitalis by depressing cardiac irritability and also by offsetting the specific loss of potassium from the heart that occurs when it is exposed to large or toxic amounts of digitalis.[4, 6, 23, 24]

The series of electrocardiographic tracings on this patient demonstrates the progression of the electrocardiographic signs of digitalis poisoning until the administration of the intravenous fluids containing potassium. After the beginning of this therapy, there was a progressive decrease in the signs of digitalis intoxication. This reversal of the progression of these signs occurred earlier than would be expected considering the peak of the effect and the length of action of digitoxin. Most reports[4, 6] on the treatment of digitalis intoxication have concluded that potassium is relatively nontoxic in the presence of normal renal function. Admittedly, the use of intravenous potassium-containing fluids is attended with more danger than oral medication, but the persistent vomiting made the intravenous route a necessity. The fluids did not contain a large amount of potassium and they were administered slowly. The use of an intravenous infusion not only afforded a vehicle in which to administer potassium ions, but it also helped to correct the fluid loss and electrolyte imbalance from the severe vomiting and cessation of fluid intake. It further helped to correct the acidosis of dehydration which itself may cause potassium loss; and it helped keep up an adequate urine volume to promote excretion of digitoxin and any excess of potassium which had been administered.

SUMMARY AND CONCLUSIONS

Although accidental drug poisoning in children is common, accidental digitalis poisoning in children is rare as evidenced by the scarcity of material in the literature on this subject. Two case reports of accidental digitalis poisoning from the British Isles are cited. These resemble our case in both the amount ingested and the course of events following the ingestion.

The patient reported here was a 2-year-old boy who ate about 1.5 mg. of digitoxin. He displayed a number of the signs and symptoms of digitalis intoxication. Serial electrocardiograms showed a progression of the electrocardiographic manifestations of digitalis toxicity which continued until the initiation of intravenous fluids containing potassium. After this there was a gradual decrease in the electrocardiographic manifestations of toxicity returning to a normal electrocardiogram three days after ingestion of the digitoxin.

The toxic effects of digitalis are discussed briefly as well as the treatment of digitalis intoxication. Although

no definite conclusion can be made concerning the effect of potassium therapy, it appeared to have had a beneficial effect on this patient, at least on the electrocardiographic signs of digitalis toxicity.

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NARCOTIC WITHDRAWAL SYMPTOMS IN THE NEWBORN INFANT RESULTING FROM MATERNAL ADDICTION

HERMAN SCHNECK, M.D.*
NEW YORK, N. Y.

DURING the past decade, narcotic addiction has received increasing attention in both lay and medical publications However, the adverse effects of maternal addiction on the newborn baby has received scant mention. It would seem appropriate at this time to stimulate an awareness of this problem because of the necessity of early appropriate treatment in the more severely addicted infants.

Murray[1] described 18 infants delivered at Sydenham Hospital in New York City during 1953, 1954, and the first ten months of 1955, born of mothers all of whom were acknowledged heroin addicts. He found that heroin addiction in the mother is frequently associated with prematurity in the baby. Fifteen babies developed withdrawal symptoms within 1 to 56 hours after birth and 4 died, a mortality of approximately 25 per cent. In addition to characteristic withdrawal symptoms such as tremors, vomiting, diarrhea, cyanosis, anorexia, and inanition, these babies developed respiratory symptoms consisting of increased production of mucus. The amount of mucus was great enough to interfere with respiration, requiring aspiration and oxygen. The babies who succumbed apparently died of respiratory failure.

From the Pediatric Service of Beth Israel Hospital, New York, N. Y.
*Address: 1175 Park Ave., New York 28, N. Y.

Five babies were treated for their withdrawal symptoms with methadone given in doses of 0.5 mg. to 1 mg. every four to twelve hours and continued in decreasing doses for several days or weeks. All of these babies survived and appeared to do better than those on standard therapy with paregoric or barbiturates.

Goodfriend and associates[2] reviewed the literature and reported 10 additional cases in 1956. They stressed the importance of making the diagnosis early so that effective therapy could be instituted without delay. It was found that the over-all reported mortality in infants varied from approximately 34 to 93 per cent, depending upon whether or not therapy was given. It is interesting to note that in 2 of their cases the presence of hepatitis in the mother presented the clue to the history of addiction. Serum hepatitis occurs frequently in addicts because of common usage of contaminated needles and syringes.

During the same year, Slobody and his associates[3] presented a series of 22 newborn infants born of addicted mothers over a period of five years. Eighteen of these women were heroin addicts and their individual daily doses varied from 2 mg. to 45 mg. Nine or almost half of the babies were premature by weight, i.e., less than 2,500 grams. The symptoms were

similar to the ones described by previous authors (Table I). They found a direct relationship between the severity of the infant's signs and symptoms and the size of the maternal narcotic dosage. Recovery took place in all the babies.

TABLE I. NARCOTIC WITHDRAWAL SIGNS AND SYMPTOMS IN THE NEWBORN INFANT

Restlessness and irritability	Inanition
Tremors	Sneezing
Convulsions	Intermittent cyanosis
Fever	Respiratory difficulty associated with increased mucus
Yawning	
Vomiting	Excessive high-pitched crying
Diarrhea	Diaphoresis
Anorexia	

No treatment was necessary in 9 cases because of the mild course. In the remaining 13, treatment included drugs such as paregoric, Thorazine, phenobarbital, and reserpine. Of these the most effective were Thorazine and paregoric. Since psychic dependence to narcotics does not exist in newborns they were much easier to cure. However, the authors advise that the most appropriate solution is removal from the mother.

Steg[4] reported 3 infants seen at the Boston City Hospital during a period of fourteen months, all of whom survived without definitive treatment. The symptoms in these babies paralleled those reported previously. She stresses the importance of the cry in these infants describing it as "louder, higher-pitched, and more continuous than the cry ordinarily observed in infants with organic disturbance of the central nervous system."

Recently, the first case of a baby born to an admitted heroin addict occurred in our hospital, the details of which follow.

CASE REPORT

Baby S. was delivered of a white 24-year-old woman who arrived at the hospital in labor. She had not had any prenatal care. Shortly after delivery, numerous needle puncture marks were noted on both her arms and forearms and, upon questioning, the mother freely admitted to being a heroin addict. She proved to be extremely uncooperative other than giving this information and disappeared from the hospital on the following day. Although she was given no Demerol and the delivery was a simple spontaneous one, the baby appeared unduly narcotized. It is quite likely that the mother had had a recent dose of heroin shortly before her arrival at the hospital. The baby's birth weight was 5 pounds, 14 ounces.

Toward the end of the first twenty-four hours the baby became very restless and irritable and developed tremors and twitchings. The classical features of tetany such as the Chvostek, Trousseau, and peroneal signs, and carpopedal spasm were absent. An initial blood calcium specimen was lost but a repeat one was normal. Calcium gluconate was given with no apparent relief. Shortly thereafter, vomiting and diarrhea occurred accompanied by constant shrill, high-pitched crying and refusal to take feedings. As a result of the restlessness, severe excoriation of the heels and knees occurred. Accompanying these symptons were a persistent nasal stuffiness, increased sweating, severe enough to produce a rash and a rise in temperature to slightly over 100° F., rectally. There were several bouts of intermittent cyanosis within the first forty-eight hours. All the symptoms subsided gradually over a period of a week to ten days at which time the infant began to thrive, taking her formula eagerly and gaining weight. She was discharged to a welfare agency at approximately 5 weeks of age, weighing 6 pounds, 9 ounces and free of all symptoms.

Since the Pediatric Service was not aware of the mother's addiction for

a few days, it was decided to withhold treatment. The infant recovered without definitive therapy although the symptoms were characteristic enough to suggest earlier inquiry about the mother. Had this been done soon after delivery the baby would undoubtedly have received medication.

DISCUSSION

It is quite possible that many cases of narcotic addiction in newborn infants have been overlooked. Since there has been an increase in drug traffic during the past decade there may well be a rise in the number of addicted mothers. Because the mortality of untreated babies is high it is important that pediatricians as well as obstetricians be aware of the withdrawal signs and symptoms in newborns so that appropriate therapy can be instituted early whenever necessary. These babies are usually irritable and restless. They cry continuously with a shrill, piercing scream. Feedings are taken poorly and are associated with frequent vomiting and diarrhea, resulting in inanition. Twitchings, tremors, and even frank convulsive seizures occur accompanied by intermittent cyanosis. This might lead one to suspect tetany or central nervous system injury. In addition, the infants present withdrawal symptoms found in adults such as yawning, nasal stuffiness, sneezing, increased sweating, and fever.

Whether the infant will develop symptoms depends to a large extent upon the time the mother had her last dose of narcotics. As Goodfriend[2] and Steg[4] have noted, if the mother has had treatment for several weeks prior to delivery, the chances of the baby having clinical signs and symptoms will be slight whereas if the parent has taken narcotics until the end of pregnancy the infant will probably show the characteristic picture of addiction.

Treatment consists in administering opiates or tranquilizers in gradually diminishing amounts over a period of days to weeks. Although paregoric and barbituates have been used by most authors, others have found Thorazine and reserpine effective. Since infants of addicted mothers are rarely nursed these days, the question of adequate secretion of narcotics in breast milk sufficient to maintain the baby free of symptoms[5, 6] is more academic than real. Furthermore, the increased emotional attachment of an addicted nursing mother toward her newborn infant would further complicate the problem of separating the child from the parent.

Although it has been implied that these infants are apparently cured completely once their symptoms have subsided it would appear that a prolonged follow-up period is in order. If some of these babies are ill enough to have severe respiratory symptoms, cyanosis, and convulsive seizures, it may be reasonable to assume that a fraction of them could be left with some residual organic brain damage. To my knowledge there are no data in the current literature dealing with this aspect of the problem.

Since many, if not most, of these babies are placed for adoption, one may ponder the question whether these infants are a good adoptive risk. Could the mother's emotional instability which led her to resort to narcotics foreshadow the neuro-hereditary pattern of her offspring—or is the infant's ultimate emotional development primarily one of environment? At any

rate, the sociological and genetic aspects of the problem assume increasing importance.

SUMMARY AND CONCLUSION

During the past decade there has been a rise in narcotic addiction. This has received increasing attention in the lay press and in scientific publications. However, there has been little mentioned of the adverse effects of maternal addiction on the newborn baby.

Abstinence signs and symptoms in these infants present a fairly characteristic picture which is not difficult to diagnose provided it is kept in mind.

The mortality in untreated infants manifesting withdrawal symptoms is high. Early diagnosis is therefore very important.

Treatment consists in administering decreasing doses of opiates, barbiturates, Thorazine, or reserpine over a period of days or weeks.

Since newborn addiction is not on a psychological basis, cure is much easier to accomplish. However, to ensure this, removal of these babies from the environment of the mother is important.

A prolonged follow-up study is suggested to determine whether any residual effects and/or organic damage from narcotic drug addiction have remained in these babies. Equally important is the evaluation of their emotional development.

The problem is not only medical but poses important genetic and social considerations. It seems appropriate at this time to bring further awareness of this to all physicians caring for the newborn infant.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
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SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THIS boy was well, save for an episode of cyanosis on the first day of life, until the age of 8 months, when he developed an upper respiratory infection with fever, cough, and wheezing. This infection lasted several days and responded to antibiotic therapy. A heart murmur was first heard at the time of this illness. At the age of 14 months he began to have tantrums, associated with episodes of cyanosis, and stiffening of several minutes' duration. From this time it was noted that he developed slight cyanosis during upper respiratory infections.

He was first admitted to The Children's Medical Center at 18 months of age because of rapid and difficult respirations. Physical examination then revealed a poorly nourished boy, below the third percentile for height and weight. The temperature was 100° F. (rectal), the pulse rate was 120 per minute, and the respiratory rate 55 per minute. The blood pressure was 150 mm. Hg systolic and 80 mm. Hg diastolic in both arms. A blood pressure of 45 mm. Hg by the flush method was obtained in the legs. The femoral pulses were weak. The chest was emphysematous, with a left-sided prominence. Râles, rhonchi, and wheezes were heard throughout both lung fields on auscultation. The heart was slightly enlarged to the left. A questionable murmur and a third heart sound were heard, loudest at the apex. There were grade II mid-diastolic and grade III systolic murmurs at the apex; the latter was transmitted to the back and axilla. A grade II systolic murmur with a faintly heard diastolic component was noted at the second left interspace and was transmitted to the cervical region. The liver was palpable 3.0 cm. below the right costal margin.

The admission laboratory data were: hemoglobin 10.5 Gm. per cent, leukocytes normal in number and differential count. The electrocardiogram was interpreted as showing auricular hypertrophy, "P-mitrale," and an incomplete right bundle branch block with right ventricular hypertrophy that was unduly marked for the age of the child. The left ventricular electrical potentials suggested combined ventricular hypertrophy. The chest roentgenograms revealed a globular heart and bilateral ventricular enlargement, the right ventricle being more enlarged than the left. There was a concavity in the region of the main pulmonary

artery with a narrow superior mediastinum. The right auricle appeared enlarged. The aorta lay on the left. The pulmonary vasculature was increased, probably on the basis of active and passive congestion.

The child was treated for bronchitis and congestive failure, with improvement. He was discharged home on Digoxin and prophylactic Gantrisin.

At age 21 months, he was again admitted with a recurrence of his fever, cough, and respiratory difficulty. A thrill was now palpated in the suprasternal notch and a grade II continuous murmur was heard below the left clavicle. The liver was 6.0 cm. and the spleen 3.0 cm. below the costal margin. No other changes in the physical examination or laboratory findings were noted. With antibiotics and Mercuhydrin, he improved and was discharged after 2 weeks of hospitalization on his previous maintenance therapy.

physical examination revealed a temperature of 98° F., respirations 32 per minute, pulse 100 per minute, blood pressure 150 mm. Hg systolic and 70 mm. Hg diastolic in the right arm, and 180 systolic and 30 diastolic in the left arm. The blood pressure was not obtained in the legs. He appeared ill and in acute respiratory distress. The chest was barrel shaped with subcostal retraction. The lung fields were hyperresonant; râles, rhonchi, and wheezes were heard throughout. The pulmonic second sound was increased, the other murmurs remaining as before. The liver and spleen were still enlarged.

Laboratory tests gave the following data: the urine was normal, the old tuberculin test negative, the blood hemoglobin level was 12.5 Gm. per cent, and erythrocytes 4.19 million per cubic millimeter. The hematocrit was 35 per cent. The leukocytes numbered 19.6

TABLE I. CARDIAC CATHETERIZATION DATA

POSITION OF CATHETER	OXYGEN CONTENT VOLUME PER CENT	OXYGEN CAPACITY VOLUME PER CENT	OXYGEN SATURATION PER CENT	PRESSURES MM. Hg AT 25 MONTHS	PRESSURES MM. Hg AT 34 MONTHS
Right auricle	11.55			4	3
Right mid-ventricle	11.70			75*/ 2†/13‡	47*/ 0†/17‡
Right pulmonary artery	11.70			70*/30†	37*/10†
Pulmonary capillary	15.40			13	12
Left axillary artery	15.25	15.4	99	150/75	120/66
Left femoral artery	15.25		99	88/56	85/62

*Systolic.
†Minimal diastolic.
‡End diastolic.

There were five admissions to a hospital in another state over the next year, for the same complaints. A cardiac catheterization was done at age 25 months (the results are listed in Table I).

His final admission took place at 34 months of age, after a further recurrence of similar symptoms. Now, the thousand with 72 per cent polymorphonuclears and 28 per cent lymphocytes on the smear. The serum globulin level was 4.7 Gm. per cent. An estimation of the concentration of sweat electrolytes was within normal values. The chest roentgenograms revealed mottled confluent densities in both lung fields, but more prominently on

the right. This was interpreted to represent chronic congestion with a superimposed infection.

Vigorous antispasmodic and antibiotic therapy was begun, and prompt clinical improvement occurred so that digitalis was discontinued, although râles and rhonchi were present in the lung. Skin tests showed him to be sensitive to a large number of antigens. A month after entry, digitalis and Mercuhydrin were administered again but without effect on the pulmonary findings or body weight. Adrenalin and cortisone were also tried for 3 days, with no effect. A repeat cardiac catheterization was performed and, ten days later, an operation was done, during the course of which he died.

DISCUSSION

DR. ALLAN L. FRIEDLICH.*—The patient had repeated severe respiratory infections with fever, cough, and wheezing, which responded to antibiotics. This profusion of respiratory infections always brings to mind, in a patient with congenital heart disease, a left-to-right shunt with an increased pulmonary blood flow. This seems to have a peculiar ability to make children more susceptible to respiratory infections. The temper tantrums, associated with slight cyanosis and stiffening for several minutes' duration, suggest spells seen in tetralogy of Fallot and tricuspid atresia, but since no further mention is made of this, I think we can omit any further consideration of it.

The blood pressure in the arms, on the first admission here, was 150/80, which I don't have to remind you is a considerable hypertension for a child of this age, although in an adult it would not be particularly alarming.

While there was hypertension in the arms, the blood pressure could not be auscultated in the legs; therefore, a flush pressure determination was done instead. This was found to be 45 mm. Hg and approximates, I am told, the mean arterial pressure in the legs, so there was a distinct pressure gradient between the arms and the legs. The femoral pulses were poorly felt. Therefore, there is certainly no question that a coaretation of the aorta was present.

The split second heart sound again calls to mind the possibility of the presence of an atrial septal defect, of which a split second sound is rather characteristic. The prominent apical third sound I interpret as a gallop, if the grade III systolic murmur which was transmitted to the back and axilla was maximal at the apex. The systolic murmur in the second left interspace is in keeping with the diagnosis of coaretation; it may extend into diastole and thus simulate a continuous murmur due to diastolic flow through the coaretation. In the presence of continuous murmur, a patent ductus arteriosus, or a so-called "pseudotruncus arteriosus," with extensive collateral circulation in the lungs must be considered. X-ray findings will rule out the latter diagnosis entirely. The grade II middiastolic rumble heard at the apex can be due to mitral valve diease; dilation of the ventricle resulting in relative mitral stenosis, as one sees in children severely ill with acute rheumatic carditis, or to a condition associated with a large pulmonary blood flow.

The electrocardiographic changes of left auricular hypertrophy focus our

*Instructor in Medicine, Harvard Medical School, and Assistant Physician at the Massachusetts General Hospital.

attention on lesions on the left side of the heart, principally coaretation or mitral stenosis. The electrocardiographic evidence of incomplete right bundle branch block and right ventricular hypertrophy, the split second sound, and the tendency toward repeated pulmonary infections all suggest the possibility of an atrial septal defect.

May we see the x-rays?

DR. MARTIN H. WITTENBORG.—The fluoroscopy revealed that the heart was enlarged to the right and the left, the atria participating in the enlargement, but Dr. Currarino felt that the right ventricular enlargement was predominant. The region where the pulmonary artery normally lies was diminished in width at all times, suggesting that the main pulmonary artery segment was either small, absent, or malposed. Since he could not find it any where else, he assumed that it was certainly either absent or hypoplastic.

DR. FRIEDLICH.—Do you think, knowing this child's clinical findings indicating coaretation of the aorta, that the appearance of a narrow waist could be produced by a small aortic knob?

DR. WITTENBORG.—In general, in coaretation, even in the presence of a hypoplastic aorta, little confusion with the pulmonary artery occurs in interpretation of the radiologic evidence. In this examination we can be sure that the pulmonary artery is not large and is probably hypoplastic. The aorta definitely lies on the left, and the ascending aorta is small. There is evidence to suggest a descending aorta on the left, but no signs to suggest a coaretation. We cannot usually visualize the coarcted segment on a routine chest film but must rely on signs of collateral circulation or post-stenotic dilatation in conjunction with the changes in heart contours. The findings here are not characteristic of an uncomplicated coaretation.

DR. FRIEDLICH.—Do you think the pulmonary blood flow is increased?

DR. WITTENBORG.—The pulmonary blood flow is hard to evaluate in this particular patient because of inflammatory changes, but it is not grossly altered.

DR. FRIEDLICH.—Do you see any cysts in the lungs?

DR. WITTENBORG.—There are inflammatory changes in the right lower lobe, mixed atelectasis and hyperaeration, but no true pulmonary cysts. In the last film taken, the inflammatory lesions have cleared.

DR. FRIEDLICH.—We have, then, both radiologic and electrocardiographic evidence of right ventricular hypertrophy, and that is going to be hard to explain.

What can we say about the catheterization data? First, we have confirmation of the clinical observation of hypertension in the upper part of the body and hypotension in the lower, with pressures in the axillary artery of 150/75, and in the left femoral artery of 88/56. It may be unwise to use the left axillary artery rather than the right because, of course, sometimes the left subclavian arery may be involved in the coarcted segment and one may not get a true value for the pressure gradient. The pulmonary capillary pressure was 13 mm. Hg, which is distinctly elevated. This means that there is some interference with the function of the left ventricle, either by

left ventricular constriction of endocardial, pericardial, or myocardial origin, or by mitral stenosis or regurgitation. One cannot differentiate which of these possibilities is responsible. The pulmonary artery pressure was 70/30, which is moderately elevated. This may be secondary to primary lung disease, to a left-to-right shunt, or to mitral stenosis. In the latter instance, the obstruction in the pulmonary arterioles may be even more important than that of the mitral valve. Since the right ventricular pressure was 75 mm. Hg systolic and that in the pulmonary artery was 70, I think we can exclude significant pulmonary stenosis. The right ventricular end diastolic pressure was 13, when the right atrial pressure was only 4, and it would be interesting also to know whether the configuration of the right ventricular pressure tracing showed any suggestion of a diastolic plateau which would suggest constriction of the right ventricle, either pericardially or endocardially.

At the last admission, the blood pressure in the right arm was 150/70, and in the left arm 180/30. Now, what do such differences mean? It is hard to do exact comparisons in pressure in the two arms, unless they can be done simultaneously. I doubt that it means an anomalous right subclavian artery arising from the aorta, below a coaretation, because the blood pressure was not obtainable in the leg—although I am always worried about what would happen if there was a coaretation involving the left subclavian.

The presence of a high normal level of gamma globulin and the normal sweat test effectively rule out agammaglobulinemia and mucoviscidosis as causes for the repeated respiratory infections. The confluent densities in the x-ray responded very quickly to a regime of antibiotics, which rules out pulmonary infarction or bizarre infections as their cause.

The child, by skin test, was allergic to a large number of antigens. This was very obviously a sick child and one who did not seem to be a good risk for surgery for coaretation. The inability to see the area of coaretation, and the possibility of other associated lesions, might very well have suggested the possibility of doing an angiocardiogram to clarify the anatomy of the situation before operation, and I would assume that the child's critical condition and also the multiple sensitivities were reasons why an angiocardiogram was not done in a patient in whom the presence of associated lesions were suspected but not established.

At the second catheter study, the oxygen content in the superior vena cava was the same as that in the right auricle, right ventricle, and pulmonary artery, ruling out any significant left-to-right shunt in the heart or into the pulmonary artery. Is there a right-to-left shunt? No, because the arterial oxygen samples were 99 per cent saturated. Is there any shunt through a patent ductus arteriosus from the pulmonary artery into the aorta, perhaps below the coaretation? Here, too, the answer is "No," because the oxygen content of the femoral arterial blood is the same as that in the axillary artery. The pressure measurements again indicate a high pulmonary capillary pressure but with less pulmonary hypertension.

I am sure that operation performed was for coaretation of the aorta. It

was undoubtedly realized that the risk in this child was very high. The results of surgery in this age group are disappointing from the standpoint of the high risk, with mortality rates of 50 to 75 per cent. The cardiac group at this hospital has made a considerable contribution by pointing out the favorable results of medical treatment of infants with coarctation who are in congestive failure. Yet, if one uses optimal medical treatment and the child is still in difficulty, operation must be seriously considered.

If this child had mitral regurgitation, the volume of mitral regurgitation would be partially dependent on the systolic pressure developed in the left ventricle. It might reasonably be hoped that by removing an aortic block and lowering the systolic pressure, the volume of mitral regurgitation would be decreased and an additional relief obtained. From the auscultatory findings and catheter data, I would think that this lesion probably involved the mitral valve. Mitral regurgitation of this sort, as an isolated defect, is rare, but can occur as duplication of the mitral orifice or fenestration of the valve. More commonly, congenital mitral regurgitation would be associated with endocardial sclerosis. Other commonly associated defects seen in coarctation are bicuspid aortic valve and atrial and ventricular defects. There is a good deal to suggest, in this case, that the lungs may have been giving him more trouble than his heart. Dr. Beecher and others have pointed out the hazards of high accumulations of carbon dioxide during thoracotomies, even with normal lungs. With pulmonary insufficiency, this would be an even greater hazard in an operation in which one lung has to be collapsed in order to get adequate exposure. I am sure that every effort was made to ventilate this child well during the operation. The underlying cause of the pulmonary difficulty here is rather hard to determine. Mucoviscidosis and agammaglobulinemia have been pretty well ruled out. A left-to-right shunt was ruled out by the catheterization studies. There is no indication of a vascular ring or other causes of respiratory tract obstruction by x-ray and no known aspiration. I suppose we would have to feel that this child has a bronchiolectasis or bronchiectasis with compensatory areas of emphysema, repeated respiratory infections, and pulmonary insufficiency on these grounds.

In summary, then, my diagnoses include coarctation of the aorta, mitral valve involvement due to subendocardial sclerosis, congestive failure, and bronchiolectasis or bronchiectasis.

DR. GUSTAVE E. DAMMIN.*—Is it assumed that the murmur was there before the age of 8 months when the murmur was first recognized? Is this a late developmental anomaly, or is it an acquired lesion although there is no suggestion that rheumatic heart disease is present?

DR. FRIEDLICH.—It appeared so early that I assumed it was congenital in origin.

DR. DAMMIN.—Was there any suspicion that the patient might have bronchial asthma, related in some way to these recurrent infections?

*Consultant Pathologist to The Children's Medical Center, Professor of Pathology, Harvard Medical School at the Peter Bent Brigham Hospital.

DR. PETER AULD.—This was our main concern. We wondered if this child had bronchial asthma. For this reason he was given cortisone. We thought that we could hear some changes in a few days in his auscultatory findings. This problem was not resolved.

DR. LOUIS K. DIAMOND.—The protocol mentioned a large spleen. You do not believe that this was the result of chronic decompensation in a patient with heart disease?

DR. FRIEDLICH.—I am sure that in adults you occasionally find the spleen a little enlarged, secondary to right ventricular failure. I would assume that children's spleens, like the liver, might be a little more distensible and you might see it more frequently. I think we do in acute rheumatic heart disease. It is somewhat unusual to have a spleen this large from congestion alone, and whether or not this has any added significance, I don't know.

DR. DIAMOND.—I have had the problem arise recently in several children with known congenital heart disease and periods of decompensation, who then developed low peripheral leukocyte, erythrocyte, and platelet levels, with splenomegaly. I wonder whether or not this is an independent development, or is it due to the enlargement of the spleen with resulting hypersplenism.

DR. PATRICK ONGLEY.—We do not often see hypersplenism in congestive heart failure—unless the liver itself is fairly large. We have one such case on the ward now.

Dr. Wittenborg, could the levels of the diaphragm have anything to do with the palpability of the spleen and liver?

DR. WITTENBORG.—The diaphragms are in normal position in the films. As far as the lungs are concerned, this is not the acute emphysema of a diffuse asthmatic process, but there are rather patchy areas, as we see in peripheral bronchial infection.

DR. DAMMIN.—Could we have the preoperative diagnosis and, then, the operative findings?

DR. AULD.—We believed that the child had coaretation of the aorta and bronchial asthma. We thought there was some other congenital anomaly, perhaps mitral stenosis, related to endocardial sclerosis.

DR. LESTER W. MARTIN.—I might say a word about the preoperative evaluation.

The first time we were asked to see this child, we refused to consider this baby for surgical treatment on the grounds that we did not think the child would withstand the operation. Dr. Gross thought that he did have a coaretation, but that other difficulties were more important than his coaretation. Finally, it became obvious that something had to be done, since he had been in and out of the hospital for about 9 months, with most of his time in the hospital and only a few days at home. We went ahead with the surgery, with the family realizing full well that the operative risk was at least 50 per cent. At surgery, we did the usual coaretation procedure. The coareted segment had a pinpoint opening just distal to the attachment of the ligamentum arteriosum. The latter was completely obliterated. After the clamps were applied, we began

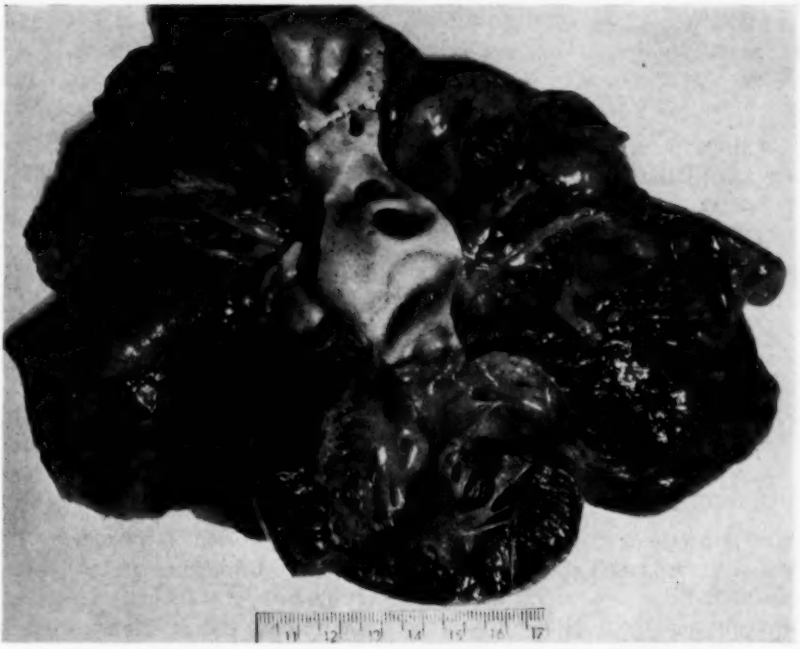

Fig. 1.—View of the left side of the heart and aorta. The anastomosis of the aorta appears intact. There is diffuse endocardial thickening and myocardial hypertrophy.

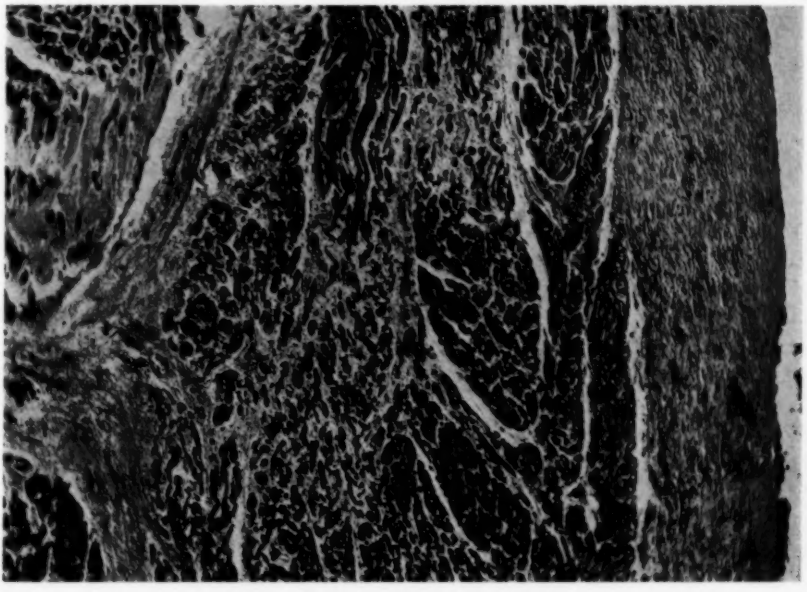

Fig. 2.—Photomicrograph of heart. The endocardium is thickened and considerable myocardial fibrosis is evident. (Hematoxylin and eosin; ×130.)

the first stitch of the anastomosis and the heart stopped beating. Cardiac massage and all resuscitative measures were of no avail.

DR. FRIEDLICH.—How much do you have to collapse the left lung in such a procedure?

DR. MARTIN.—You proceed with the operation with a fair amount of aeration of the left lung, collapsing it to 40 to 50 per cent. During the operation, if the heart begins to slow down, aeration may be increased for a period until things are in better shape. Just before we started the anastomosis, this lung had been collapsed for thirty to forty minutes.

DR. ALEXANDRE CARDOSO.—This patient had a number of congenital anomalies of the heart. The heart was markedly enlarged, bilaterally. The myocardium of the right ventricle measured 6 mm. in thickness, which is about twice normal. On the left it was 1.2 cm. in thickness. The tricuspid valve was free of any change, but there was a patchy thickening of the endocardium of the right atrium, which was markedly dilated. The pulmonary artery was 6 cm. in circumference and was dilated. The left atrium was also moderately to markedly enlarged with marked thickening of the endocardium, which was glistening white. There was a marked thickening and stenosis of the mitral valve, which measured 3.6 cm. in circumference (Fig. 1). The finger of the prosector would not pass through its orifice in the intact state. These valves were also involved by the thickening of the endocardium of the cusps with great shortening of the chordae tendineae. The endocardial surface, throughout the left ventricle, was markedly thickened, with a gray to gray-white discoloration. This appearance was borne out microscopically (Fig. 2). The aortic valve was bicuspid, with only partial formation of the septa in one of the cusps. This cusp contained two coronary ostia. The aortic arch was hypoplastic, measuring 3.6 cm. in circumference. The anastomosis was intact, and no leakage was present. There was no evidence of a patent ductus arteriosus. The lungs were markedly collapsed; the left lung occupied approximately 20 per cent of the pleural cavity and the right about 35 per cent.

The lungs were congested, with areas of bronchopneumonia. There was some thickening of the basement membranes of the bronchioles, as is seen in patients who die with asthma.

DR. DAMMIN.—In regard to the changes in the lungs, we would have to say that, if this patient did have bronchial asthma, there was no evidence that it was active at the time that he died. There were very minimal changes in the form of basal membrane thickening in the bronchi, but there was no eosinophilic infiltration and actually no microscopic or gross evidence of any prolonged evidence of obstructive episodes. We know that recurrent infection with exudation can lead to almost the same anatomic changes by the same mechanism for obstructive emphysema that bronchial asthma can, but we found no such evidence here. Therefore, we would say that this was a recurrent pulmonary infection, possibly related to a minimal degree of myocardial failure and pulmonary congestion, and that there was

no other anatomic evidence here for any other lesion of the recurrent pulmonary infection.

The endocardial lesion is important. Although this can be acquired in some degree, here it is probably one of the developmental anomalies that has a great deal to do with myocardial function. Most of these patients, when they do succumb, succumb after a very short illness—usually of congestive failure, once the lesion makes itself apparent. It is interesting to note that valvular deformities are common with endocardial sclerosis, and actually most instances of congenital mitral stenosis and insufficiency are associated with endocardial sclerosis, so that in this situation one would suspect (from the clinical findings here) that endocardial sclerosis and a mitral deformity would be associated. It is interesting, also, that with this group of changes there are rarely any extracardiac congenital anomalies. There are multiple anomalies within the heart and greater vessels but, in contradistinction to the septal defects, there are very few (if any) extracardiac anomalies associated with these deformities of the type seen in this case, so that everything of importance that was observed at post-mortem examination was recognized clinically by Dr. Friedlich.

Medical Progress

RHEUMATIC PNEUMONIA

GEORGE BROWN, M.D.,* DAVID GOLDRING, M.D., AND M. REMSEN BEHRER, M.D.
ST. LOUIS, MO.

WHEN one considers the protean manifestations of rheumatic fever, it is not surprising that the lungs may be involved by the inflammatory process. Yet, when standard textbooks or published reports are consulted, much controversy and skepticism about this rheumatic manifestation are encountered. Even though rheumatic fever is considered a childhood disease, there is a paucity of information in the pediatric literature concerning the pulmonary manifestations of rheumatic fever. Only 5 references were found in exclusively pediatric journals.[19, 24, 56, 68, 99] The last comprehensive review on the subject[75b] was published in 1928 prior to the introduction of the sulfonamides, antibiotics, and the hormones, ACTH and cortisone.

The material presented consists of a review of the available publications about rheumatic pneumonitis. Articles are now in press, presenting (1) an analysis of the clinical and laboratory data on 23 patients with rheumatic pneumonitis, of which 21 were observed by one of the authors, and (2) a study and review of the pathologic findings in 87 fatal cases of rheumatic fever in children ranging in age between 3 and 16 years, who were patients at St. Louis Children's and Barnes Hospitals during the period 1919 through 1954.

*Present address, Indianapolis, Ind.
From the Department of Pediatrics, Washington University School of Medicine, St. Louis Children's Hospital.

HISTORY

In the classic review on the subject of rheumatic pneumonia, Paul[75b] stated that descriptions of polyarthritis date back to the time of Hippocrates. The valuable and most acceptable descriptions of the rheumatic syndrome date from the early seventeenth century. Paul attributed the first use of the word rheumatism to a physician in Paris, Guillaume Baillou or Ballonius, who lived from 1538 to 1616. The word rheumatism had been used previously in the sense of a weakness or indisposition, but Ballonius[3] used it to describe a condition with fever and polyarthritis which he thought could be differentiated from chronic arthritis and gout. Sydenham, in 1676, described accurately what we know as rheumatic fever and differentiated it from gout. He recognized that internal organs were affected, but said nothing specific about cardiac or lung involvement. Boerhaave[8] in 1737 referred to Sydenham's description as the best that he could find. In his description,

Boerhaave stated that the disease invades "sometimes the brain, lungs and bowels." Störek[96] in 1762 recognized the wandering nature of the malady and also recognized that the internal organs as well as the joints were involved. He described patients with oppression of the chest, cough, and other symptoms which suggest cardiac or pulmonary disease. Störek also wrote about the earliest autopsy examinations to be found on patients with rheumatic fever. He recognized pleurisy and compression of the lungs without recognizing the cardiac lesions. Lettsom[55] in 1787 described an autopsy on a child who died of acute rheumatism with pericarditis and pleural fluid, without recognizing the associated cardiac lesions. Stoll[95] in 1788 wrote of pleural fluid in rheumatism and used the term "rheumatic peripneumonia" without giving any pathologic descriptions. Later, French writers gave little mention of his works. Chomel[15] in 1813 mentioned pulmonary involvement with rheumatism, mostly pleurisy, but was cautious not to associate them, and rather thought that the arthritis and the pleurisy were "separate afflictions." Balfour[2] in 1816 stated definitely that rheumatism was a generalized disease of fibers and membranes throughout the body, and that every blood vessel had a coat of this membrane down to the capillaries. Writing in 1840, Bouillaud[9] recognized pleurisy as a rheumatic manifestation and wrote freely about it. Grisolle[39] thought pleurisy associated with the rheumatic cardiac lesion was quite common, but pneumonia quite rare. Latham[52] in 1845 was clearly of the opinion that pneumonia occurred with rheumatism, and in a series of 136 cases of acute rheumatism, mentioned 24 with lungs "inflammed"; 18 cases were classed as pneumonia on clinical grounds. Wunderlich[107] in 1856 reported that over 6 per cent of 108 patients with rheumatism had pulmonary or pleural lesions. He discussed many clinical varieties of rheumatism. Ormerod[73] wrote in 1858 that lung involvement was a complication of rheumatism, and was usually active in causing death in such cases. Seventeen of his 61 patients had "pneumonia" and 4 of these died (no autopsy reported). He thought of the lesion as "collapse" rather than the "splenization" or "congestion" described by others. He also stated that pericarditis was a necessary accompaniment of rheumatic pneumonia. Therapy was considered useless. Vulpian[101] in 1860 described the pulmonary lesion as probably just collapse. Lebert[53] in 1860, in the German writings, recognized the pneumonia, but thought it was very rare, occurring in 1.4 per cent of 140 clinical cases. He wrote of pleurisy with accuracy and was impressed that it occurred much more frequently than pneumonia. Fuller[29] in 1864 reported 246 cases with clinical findings of pneumonia in 19, with a much larger number showing signs of pleurisy or bronchitis. He noted some pulmonary pathologic findings in almost all fatal cases of carditis. Of 16 autopsies, pneumonia was found in only 2 cases. Fuller also mentioned a case of peritonitis occurring with rheumatism. Of 41 cases, Gull[40] in 1865 found 6 with pulmonary complications, only one of which might have been pneumonia. In 1873 Pye-Smith[80] found 7 cases of pneumonia in 400 cases of rheumatic fever, 5 of which proved fatal. He regarded the pneumonia as an accidental complication of the disease,

rather than an integral part of it. Sturges (quoted by Garrod[31]) in 1876 attributed the pulmonary involvement in rheumatism to two factors of that condition: (1) congestion of the lungs due to poor heart action, and (2) the fibrinous character of the blood itself which gave it a tendency to form exudates, or consolidation. Besnier[7] in 1876 credited Pitcairn (1788) as the first to associate the carditis with the rheumatism. Besnier thought the pulmonary "splenization" was an integral part of the disease and not a "complication." He thought this manifestation might be due to the cardiac lesion, however. Bernheim[6] in 1877 discussed rheumatic pneumonia, but did not distinguish between congestion secondary to cardiac failure and true pneumonitis. Peacock[76] in 1879 discussed 394 cases with 6 deaths; in one of the latter cases there were "hemorrhagic blocks" in the lungs. Pneumonia was not mentioned in any detail. Southey[93] in 1879 presented 51 patients with rheumatism, 4 of whom had clinical pneumonia. All 4 of these recovered within 6 days, none died. A bit later, in 1885, Lebreton[54] studied the pleural lesions with little attention to the pneumonia. Longstreth[57] in 1882 thought that the pulmonary affection spread from the pericardium. The pneumonia he encountered was usually mild and associated with pleurisy. He described only one autopsy with the finding of pneumonia, in which he stressed the fibrinous character of the exudate. He thought that pleurisy could occur independently of cardiac involvement. Lasegue[51] in 1884 is credited with the well-known expression that rheumatic fever "licks the joints, the pleura and meninges, but bites the heart." Mackenzie[60] in 1886 presented 133 cases and commented on the many unanswered questions about rheumatism, many of which remain currently unanswered. He commented on the cardiac and pericardial findings without associated symptoms of arthritis. Cheadle[14] in 1888 discussed an outbreak of rheumatic fever and reported 6 patients with pneumonia, and one death. The left lung was said to be "consolidated." He stressed the importance of examination of the back, even if it caused discomfort to extremely ill patients. He also distinguished between the pleurisy of longstanding heart disease (thought to be due to mechanical congestion) and that of acute rheumatic fever. Garrod[31] in 1890 reviewed several large series of rheumatic patients and found that pneumonia was encountered in 1.52 to 13.23 per cent. He thought that the pulmonary findings could be the first event in the rheumatic disease. He described the pneumonia as not substantially altering the clinical course, nor, unless severe, the prognosis. He included a discussion of acute pulmonary edema as a different entity. In 1899 Pribram[79] reported 627 cases of rheumatic fever, 4 with pneumonia, an incidence of 0.64 per cent. There was one post-mortem examination. McCrae[63] in 1903 reviewed 270 patients with acute rheumatism, among whom he found one case of clinical lobar pneumonia. Mosler[67] in 1910 stressed the generalized nature of the affection, using the term "polyserositis rheumatica." He also added the meninges and the peritoneum to the list of serous membranes affected. He did not stress the presence of pneumonia. The generalized vascular involvement in the disease was revealed

by histologic studies by Klotz[49a, b] in 1912. He stressed the possibility of aneurysms on the basis of rheumatic involvement; he also found almost constant lesions in the ascending aorta. Poynton,[78] writing in 1913, thought that the etiologic agent was definitely established as the *Pneumococcus rheumaticus* and discussed it thoroughly. He spoke of bronchopneumonia surrounded by collapse; he also mentioned the presence of infarcts in the lungs. He thought that pulmonary edema was extremely rare and occurred only in children. Naish[70] in 1928 was the first to describe the histologic appearance of what we think of as rheumatic pneumonia. He considered the lesion to be specific, so specific as to suggest a specific virus. He stated he could find no earlier descriptions. Naish thought some of the changes might be early Aschoff nodules. He described many hemorrhagic alveoli, and used the term "India rubber" in describing the gross appearance of the lungs. He thought that pericarditis was not a necessary accompaniment of the pneumonia.

INCIDENCE

Accurate data concerning the incidence of pneumonia in rheumatic fever are not available. There are many reports of the clinical incidence based on the physical findings and symptoms. On the other hand, every victim of this manifestation does not die, so autopsy figures are not strictly applicable either.

A summary (Table I) of the earlier clinical reports should be adequate to point out the nature and order of magnitude of the findings.

In 1885 Howard[45] reviewed 920 published cases with the following findings: pleuritis, pneumonia, or bronchitis was recorded in 10.5 per cent of recent endocarditis cases; 58.0 per cent

TABLE I. SUMMARY OF EARLIER CLINICAL REPORTS

	CASES	PLEURISY	%	PNEUMONIA	%
1844 Taylor[97]	89	3	3.4	3	3.4
1856 Wunderlich[107]	108	5	4.6	7	6.5
1858 Ormerod[73]	61	7	11.5	17	27.8
1860 Lebert[53]	140	–	–	12	1.4
1864 Fuller[29]	246	13	5.3	28	11.4
1865 Gull[40]	41	5	12.5	1	2.5
1873 Pye-Smith[80]	400	18	4.5	7	1.8
1876 Latham[52]	136	3	2.2	18	13.2
1879 Peacock[76]	394	–	–	Not mentioned	
1879 Southey[93]	51	–	–	4	7.8
1888 Cheadle[14]	157	1	0.6	1	0.6
Three month outbreak:	26	1	3.8	6	23.2
1890 "Collective"[31]	655	13	2.0	11	1.5
1903 McCrae[63]	270	6	2.2	1	0.4
1920 Rolly[87]	3620	88	2.5	51	1.4
1927 Schwartz[88]	53	–	–	5	9.5
1928 Howard[44]					
Arthritis	96	7	7.3	0	0.0
Rheumatic cycle	130	20	15.3	6	2.7
1931 Coburn[17a]	162	8	4.9	11	6.8
1933 Howard[43]	489	–	–	9	1.8
1945 Plummer[77]	54	(Streptococcal sore throat)		1	1.9
1947 Rantz[82]	69	(Poststreptococcal state)		3	4.3
1947 Sokolow[92]	–	–	–	–	2.0
1954 Reimann[84]	"Severe rheumatic fever"		–	–	1.0

of pericarditis cases; 71.0 per cent of endopericarditis cases; and 7.0 per cent of cases without heart disease.

The incidence in pathologic material varies considerably depending on the rigidity of the criteria used in making the diagnosis. Many series were reported in which only the gross specimens were evaluated (Table II).

In spite of the inadequacy of available figures it has been frequently mentioned that pneumonia is an important manifestation of rheumatic fever, and an important contributor to the death of these patients. Gouley[33] stressed that the pulmonary involvement was as frequent as the cardiac involvement. Griffith[37] said that pulmonary disease is second only to carditis in importance. It might be stressed that pneumonia is not frequently seen in a series of patients with moderately severe clinical rheumatism, but that it is very likely to be

TABLE II. INCIDENCE OF PNEUMONIA IN REPORTED SERIES

	CASES	FINDINGS
1925 Thayer[98]	25 fatal cases of rheumatic fever 10 with "terminal pneumonia"	Incidence 40% Lungs were poorly studied histologically
1928 Paul[75b]	30 deaths	10-50% with pneumonia
1929 McClenahan[62]	28 fatal cases of rheumatic fever	Pleurisy 64% Pericarditis 75% Hemorrhagic pneumonia common Bronchopneumonia "uncommon" Infarction in lungs 21.4%
1933 Coburn[17b]	320 deaths	45 (14.1%) had "hemorrhagic pulmonary solidification"
1941 Epstein[23]	14 deaths during first attack	7 had "hyaline membranes" 50%
	10 deaths in cases with previous attacks; died in less than 3 weeks	5 (50%) had pneumonia
	11 deaths in cases with previous attacks; died in 3 to 6 weeks	4 (36.3%) had rheumatic pneumonia 5 (45.5%) had bacterial bronchopneumonia
	10 deaths in cases with previous attacks; present attack over 6 weeks	2 (20%) had "hyaline membrane" 5 (50%) had bacterial bronchopneumonia
1946 Griffith[38]	Reported the following percentages without giving his criteria for diagnosis of pneumonia:	

	RHEUMATISM	PNEUMONIA	
Acute fulminating	52	28	53.1%
Polycyclic	281	77	27.4%
Monocyclic, subacute	667	14	2.0%
			11.3% of total

1944 Neubuerger[71]	63 post-mortem examinations	8 (12.7%) had distinctive microscopic changes of rheumatic pneumonia

found in patients who die of acute rheumatic fever.

ETIOLOGY

As early as the eighteenth century it was implied that the whole body was involved in the rheumatic disease,[3] but this probably merely represented a statement of opinion in terms of the humoral theory of disease and did not indicate insight into what we now think of as a generalized vascular disease.

In the evolution of the more recent concepts of the etiology of rheumatic fever it is to be expected that a microbic or viral etiology would be suspected. Without implying that any specific organism or process was involved, Longstreth[57] in 1882 was the earliest to speak in terms of "spread" of the disease. He thought that the lung involvement was an "extension of inflammation from pericardium to lung." Burnet[10] in 1947 called attention to the fact that he had stated in 1905 that "pneumonia may be caused by the specific organism of rheumatism." Coombs[20a] stated definitely in 1909 that rheumatic fever must be a "microbic" disease. Just a few years later, in 1913, Poynton and Paine[78] produced a large monograph in which they described the discovery and bacterial characteristics of an organism, *Diplococcus rheumaticus,* which they were confident was the specific etiologic agent of rheumatism. Hutchison[46] in 1922 also wrote that the pneumonia was an extension to the lungs, and was always associated with pericarditis, the implication being that an organism of some sort performed the extension.

Schwartz[88] wrote of rheumatic fever producing a vulnerability to infection or reactivation of a latent infection, without specifying what sort of organism might be involved. Naish[70] in 1928 disagreed with the belief in the necessity for extension of the disease from the pericardium, or even for the necessity of concomitant pericarditis to occur. He thought that the disease was caused by a virus. Rabinowitz[81] spoke just of the rheumatic virus in 1926, two years earlier than Naish. More recently, Geever[32] in 1951 and Shopfner[91] in 1952 have mentioned the possibility of rheumatic pneumonia being the result of a virus infection. Neither bacterial nor viral studies, however, have ever been fruitful in establishing a microbic, infective agent as having a significant role in rheumatic fever or the characteristic pneumonia sometimes accompanying rheumatism.

Melnick[65] wrote that the pathologic findings had some resemblance to allergic granulomas. Rich[85] also thought that the pathologic findings were quite similar to those of sulfonamide anaphylactic pneumonia. Cook[19] thought that perhaps some nervous control of the lungs was altered by the frequently associated pericarditis.

Currently there are diverse opinions concerning the etiology of rheumatic pneumonia. The most likely were mentioned by Seldin[90]:

1. The pneumonia is a part of the rheumatic process.
2. The pneumonia is secondary to the cardiac lesion or cardiac failure.
3. Intercurrent infection is the basis for the pneumonia.
4. The syndrome is a combination of No. 1 and No. 2.

As early as 1816 Balfour[2] wrote that rheumatic fever was an affection of the muscular fiber or of "cellular membrane" which coats all the blood vessels of the body, even the "minutest capillary." Rolly[87] in 1920 wrote of the disease as a disease of the serous membranes. He thought it could not be considered as a "complication" but was an integral part of the rheumatic disease. Pappenheimer[74] in 1927 emphasized the presence of specific rheumatic lesions in peripheral blood vessels which he thought were as characteristic as the Aschoff nodule in the heart muscle. Gouley[33a] in 1937 wrote that the lungs were probably as commonly involved in the rheumatic process as the heart. He mentioned several reasons, however, why the cardiac lesion might be deleterious to lung function on a mechanical basis. Epstein[23] in 1941 thought that many of the pathologic findings in rheumatic lungs were attributable to capillary vascular damage.

Because of the usual intimate concurrence of pneumonitis with carditis, many writers have stressed that the pulmonary findings, mostly clinical, are secondary to cardiac functional impairment. Besnier[7] reported in 1876 that the pneumonia probably was not a true pneumonia, but pulmonary engorgement or "splenization," secondary to the heart lesion. Garrod[31] in 1890 studied 1,066 cases of "acute pneumonia" and found cardiac valvar lesions in only 10. He thought this was evidence that the pneumonia of rheumatism had little connection with the cardiac involvement of that disease. Although Coombs[20b] in 1924 listed collapse as a separate phenomenon from pneumonia, he pointed out that many cardiac disturbances could produce the physical signs of pulmonary disease. The frequent finding of left lower lobe collapse he attributed to either: (1) pressure from the enlarged heart on the lung, (2) immobility of the diaphragm produced by a reflex from the inflamed pericardium, or (3) atelectasis due to pressure on bronchial structures. He was careful to warn about the danger of confusing atelectasis with true pneumonic consolidation. Findlay[24] in 1930 presented 25 clinical cases of rheumatic fever with pulmonary complications. He was convinced that all cases had associated carditis, and that the pneumonia which he occasionally encountered was a "complication," either bacterial lobar pneumonia or terminal hypostatic bronchopneumonia. Interestingly enough he characterized the pleural fluid as a "transudate," in disagreement with most descriptions of this fluid. Gouley[33a] in 1937 attributed the basal pulmonary collapse to several associated difficulties seen in the patient with acute rheumatism, i.e., pleural effusion, pericardial fluid, diaphragmatic paralysis, supine position in bed, and/or cardiomegaly.

As far as the concept of the pneumonia as a bacterial infection is concerned, there is no clinical, cultural, or pathologic evidence to support such an etiology if one confines himself to the characteristic picture of rheumatic pneumonia. Surely some patients with terminal rheumatic fever must have bacterial pneumonia; patients with pulmonary edema are prone to have secondary bacterial infections. Paul[75b] and Gouley,[33a] however, both stress the fact that a bacterial pneumonia is distinctly uncommon in autopsy examination of patients who die of acute

rheumatic fever, even before the use of antibiotics.

Most pathologists who have written on rheumatic fever or rheumatic pneumonia seem to lean to the theory that all the manifestations of rheumatic fever are a reflection of a vascular reaction of some unknown type, probably hypersensitivity, and probably related in some way to hemolytic streptococcus infection. Keefer[48] and more recently Rantz[82] in 1947 have written of the protean clinical findings which they term the "poststreptococcal state." Currently we must await more specific information about the complicated serologic and cellular mechanisms which produce the full-blown, catastrophic, explosive rheumatic syndrome at times, and the limited, migratory, protean "poststreptococcal" syndrome at other times.

CLINICAL FEATURES

It is impossible to define a clinical syndrome which would be specific for rheumatic pneumonia. The circumstances which would call the clinician's attention to such a possibility would be pulmonary complications in a child with known rheumatic fever presenting with carditis, arthritis, chorea, or some other definite rheumatic manifestation. Seldin[90] stated that carditis must always accompany rheumatic pneumonia. Some observers, however, have found pneumonic involvement characteristic of rheumatic fever, but without evidence of other elements of the rheumatic syndrome.

Descriptions of the disease often stress the paucity of signs and symptoms compared with the pathologic or roentgen-ray changes found. Writing in 1888, Cheadle[14] discussed 6 cases of pneumonia associated with rheumatic fever. In 5 of the 6 there was "no cough, no rusty sputum, nothing but the rise of temperature and quickened respiration." He warned the clinician, "whenever pericarditis arises in the course of rheumatic fever, or whenever an unexplained rise of temperature, or persistence of high temperature occurs, make a careful examination of the physical condition of the chest, behind as well an in front." Garrod[31] also warned that the back should be examined in the patient with rapid rise in temperature, often transitory, without cough or sputum. Rabinowitz[81] counseled that examination of the back should not be neglected in acute rheumatic fever.

The majority opinion is that it is necessary to have diagnosed rheumatic fever in the acute stage before one can safely diagnose rheumatic pneumonia. Several authors have stated, however, that pulmonary alterations by the rheumatic process can occur as isolated manifestations in rheumatism. Gouley[33a] stated that the "involvement of the lung to some degree in rheumatic fever is as common as that of the heart." He thought that the pulmonary changes were not a complication, but rather an integral part of the rheumatic process, which might precede or occur without arthritis. Goyena[35] reported his experience of finding lung manifestations preceding rheumatic arthritis and endocarditis. Lees[59] reported 2 cases of pulmonary consolidation occurring with acute polyarthritis, but without cardiac involvement by clinical and electrocardiographic evaluation. One of the 2 patients later appeared with mitral valvar disease, however. Rabinowitz[81] thought of

rheumatic pneumonia as a special pneumonopathy usually occurring with pancarditis, but occasionally occurring in the absence of arthritis or carditis. Rantz[82] reported 3 cases of pneumonia occurring in the "poststreptococcal state." One patient was without arthritis, one had only pain in the chest, and the third had no physical signs at all, but was found to have patches of infiltration in the roentgenogram of the chest. Van Wijk[99] reported 3 cases; in the only survivor the onset of the illness was with pulmonary symptoms. Thus it appears that it is not always necessary to have a classic rheumatic syndrome with carditis before involvement of the lungs with pneumonia.

Once the lungs have been involved by the pneumonic process the clinical features are so variable and descriptions so at odds that one can only mention some of the features which previous writers have stressed. It would be useful to the clinician to know in which type of case pneumonia would be most likely to occur.

Griffith and associates[38] are the only writers who made a systematic attempt to analyze the type of rheumatic fever which is likely to be associated with pulmonary involvement. They found that pneumonia was encountered (their criteria for diagnosis were not given) in 53.1 per cent of cases of "acute fulminating rheumatic fever," in 27.4 per cent of "polycyclic" rheumatic cases and in only 2.0 per cent of "monocylic, subacute" cases. Their over-all incidence was 11.3 per cent, a widely quoted figure. Elsewhere in the literature there is little or no mention of the type of case where the suspicion of rheumatic pneumonia must be increased. Reimann[84] stated that it occurred in a small proportion (1 per cent) of "severe rheumatic fever" patients.

There is mentioned a peculiar disproportion between the change in the clinical condition of the rheumatic patient who has developed pneumonia and the physical findings which might be encountered. Often a thorough examination of the chest by routine physical diagnostic techniques reveals nothing to explain the sudden change in the temperature, respiratory rate, and cough.

Cough is a frequently mentioned symptom. Usually it is hacking in nature and without production of sputum.[90] A small number of writers have minimized the cough. Reich[83] stated that cough and sputum were not prominent. Coburn[17a] thought of the pneumonia as a solidification "without cough or sputum." In fact, he minimized the clinical changes with the description that the pneumonia was a "migratory, pulmonary solidification which appeared during severe acute carditis, not resembling pneumonia of known bacterial origin, not accompanied by cough or sputum in most instances, not associated with heart failure or atelectasis due to compression."

The absence of sputum, even where cough is present, is universally agreed upon. If a small amount of sputum is produced, it may be blood streaked or rusty.[90]

Tachypnea is probably the most common and most characteristic indication that a pneumonic process is occurring in a patient with rheumatic fever. The tachypnea may be accompanied by profound distress (dyspnea)

if the process is fulminating and overwhelming,[90] or it may be present without disturbing the patient's comfort at all.

So filled with inconsistency are the descriptions that Coburn[17a] thought there was no effect on the respiratory rate; Howard[43] thought there was a "slight elevation in respiratory rate." Conversely, Wilson[105] classed the increased respiratory rate with the fever and cough as important clinical changes when pneumonia occurred. Cheadle[14] said there may be "no cough, no rusty sputum, nothing but the rise in temperature and quickened respirations" to signal the pneumonia.

Other observers were impressed with the dyspneic respirations. Fuller,[29] writing in 1864, characterized the disease as "attacking sometimes one, sometimes another part of the pulmonary structure, sometimes invading all parts simultaneously, producing dyspnea, suffocation and death." On the other hand, Hadfield[41] stated that usually dyspnea was absent, or was seen only in the presence of congestive heart failure. In 1950 Lustock[58] wrote of the septic fever, hemoptysis, dyspnea, and orthopnea which were out of proportion to the physical findings and which did not occur with congestive failure, did not respond to digitalis or mercurial diuretics, and were not the result of overdosage of salicylates.

The occurrence of pleuritic pain as a symptom is in some question also. Garrod[31] stated that pleurisy is the "earliest even in the rheumatic series." One must be careful in evaluating pleuritic pain because many rheumatic manifestations could produce such pain without the presence of pneumonia, i.e., pericarditis, pleuritis, or pulmonary infarction. Gouley[33a] thought that pleural pain was rare. Longstreth[57] thought pleurisy was more common than pneumonia. In 1882 he said, "the gravity of the condition [pneumonia] was of slight character and usually associated with pleurisy." Myers[69] found pulmonary involvement in addition to the pleurisy in 5 of 13 cases of rheumatic pleurisy. He stated that the dyspnea and orthopnea were out of proportion to the physical findings. Seldin[90] stressed pleuritic pain as a differential point favoring rheumatic or bacterial pneumonia as opposed to pulmonary edema.

Although a classic symptom of bacterial pneumonia, chill is rarely or never found in rheumatic pneumonia.[33a]

In cases of acute rheumatic fever with generalized involvement one must be aware of the unusual complications of peritonitis[29, 83] on a rheumatic basis, or even cerebral involvement.[102]

The physical examination is often of little more aid than the enumeration of the symptoms of the patient. Descriptions are filled with such terms as shifting, evanescent, migratory, transient, insidious, fleeting. Neubuerger[71] in a review in 1944 wrote of the disease as a suddenly occurring one with fever, cough, bloody sputum, and elevation of white cell count, and severe dyspnea. Ormerod[73] in 1858 wrote that the general condition of the patient grew worse, and he thought that signs of pericarditis accompanied the pulmonary signs. Fever of greater severity than is usually seen in the patient with acute rheumatism is widely described.[90] Gouley[33a] and others stressed the suddenness of the increase in temperature. Naish,[70] however, minimized the prevalence of change in temperature.

The pulse rate probably depends more on the underlying cardiac disease than on the pneumonic process. Coburn[17a] stated that the pulse is little altered by the rheumatic pneumonia.

The majority of descriptions of the clinical findings mentioned the fleeting nature of the pneumonic involvement. Caffey[11] said the roentgen-ray shadows are "fleeting and migratory." Coburn[17a] termed the pneumonia "flighty" and thought that it usually "disappears completely before death." Epstein[23] stated there is "rapid disappearance of symptoms within a few days" with a migratory and fleeting character to the consolidation. In 1890 Garrod[31] stated the pneumonia was "transient." Others[33a, 34, 37, 43, 58, 59, 81, 83, 84, 105, 131] specifically commented on the transient, migratory nature of the pulmonary involvement. Lees[59] did differentiate a more severe, more extensive consolidation of the lower lobes which may last for weeks or months. Melnick[65] concisely summarized the usual description as "migratory, areas of consolidation in the lung fields which appear suddenly, last a variable length of time, disappear as quickly and unexpectedly as they appear, and produce no change in the clinical picture and no variation in the pulse or respiratory rate."

Whether the physical findings in the chest indicate congestion or solidification or other pathologic conditions is open to variable opinions. Coburn[17a] characterized the pulmonary features of rheumatic fever as solidification. Gouley[33a, 34] indicated that the physical findings were those of consolidation, but that the roentgenogram interpretation was frequently that of "pulmonary congestion." Lustock,[58] in a discussion of clinical and pathologic correlation, stressed the difficulty of clinical diagnosis, but referred to pulmonary consolidation.

The distribution of the lesions as determined clinically is commented on by a number of writers. Bamberger[4] in 1857 described a patch of dullness on the left posterior chest at the angle of the scapula which spread over the left base in cases of pericarditis, pleuritis, and collapse. No mention of pneumonia was made, but later writers mentioned Bamberger's sign in connection with pneumonitis of the left lower lobe. Longstreth[57] in 1882 said that the left side was more frequently involved than the right, but offered no explanation for this. Naish[70] mentioned Bamberger's sign only to contradict the impression that the left was more vulnerable. He warned against stressing one-sideness. His conclusions were supported by autopsy findings. Griffith[37] described small areas of dullness with decreased breath sounds which might occur anywhere in the lungs. Lees[59] in 1952 discussed the rheumatic lung as following two courses. One was an extensive consolidation usually in the lower lobes and lasting weeks to months; the other was focal, multilobular, evanescent, migratory in nature; and either might produce death. Gouley[33a] stressed basilar collapse, probably more frequently seen on the left. This collapse was attributed to inflammation with loss of elasticity, air absorption, and contracture, caused by interstitial pneumonitis. Other manifestations of the diffuse rheumatic condition which could lead to basilar collapse are effusion, pericardial fluid, cardiomegaly, collapse secondary to bed rest, and/or

poor diaphragmatic movement on the pleuritic side. All such factors must be considered in the rheumatic patient with abnormal pulmonary findings. Earlier Gouley[34] had described 9 fatal cases with consolidation in 8, without the demonstration of preference for any particular lobe.

The signs and symptoms of cardiac decompensation are similar to those generally ascribed to pneumonia in rheumatic fever. Coburn[17a] stated that the pneumonia was found in the absence of heart failure or atelectasis. Garrod[31] in 1890 mentioned the left-sided occurrence of pneumonia or "compression," but discussed acute pulmonary edema as found in heart failure as a separate entity. Gouley[33a] thought that usually heart failure was absent. Fraser[27] stated that the signs and symptoms are usually attributed to other diseases than rheumatic pneumonia, such as cardiac failure, pleural effusion, paralysis of the diaphragm, or pressure on the lung by heart or fluid. On the other hand, Seldin[90] thought that cardiac failure was present to some degree in all patients with rheumatic pneumonia.

As in all cases of rheumatic fever, the involvement of the heart is to be feared. Pneumonic involvement may occur with or without cardiac involvement, but, without the heart changes, a clinical diagnosis is very weak. Rabinowitz[81] stated that the pneumonitis usually occurs with pancarditis, but could be independent of arthritis or carditis. Howard[45] stated in 1885 that about 7 per cent of patients had pulmonary affections without cardiac disease. He described the evanescent and obscure findings in rheumatic pneumonia, but he pointed out that in rare instances the pneumonia definitely alternated with arthritis in the rheumatic patient. Jensen[47] reported a case of rheumatic pneumonia without carditis.

Cyanosis is rarely mentioned as a dependable indication of the pneumonic process. Seldin[90] is alone in stating that cyanosis is constantly present, along with dyspnea and orthopnea.

Pulmonary complications of rheumatic fever which might be confused with pneumonia and which should be searched for in the patient with acute rheumatism are numerous. Coombs[20b] discussed pleurisy, basal collapse, acute pulmonary edema, as well as pneumonia. Findlay[24] studied the conditions which occur with rheumatic pericarditis and listed several cases of pleural effusion, lobar pneumonia, and passive congestion, but did not believe in the entity of a true rheumatic pneumonia. He stated that pulmonary complications do not occur without carditis, but it must be noted that his approach was to study carditis rather than other conditions of the thoracic viscera. Rabinowitz[81] thought of pneumonia as a separate entity but listed many possible manifestations of pulmonary disease to be aware of in severe rheumatism: fibrinous pleurisy, pleurisy with effusion, atelectasis with or without effusion, hydrothorax secondary to cardiac failure, acute pulmonary edema, chronic passive congestion, hemorrhagic static infarction of the lung, or embolic infarction of the lung.

Widal[104] made a unique suggestion that it was possible for the rheumatic process to involve the veins of the lower extremities and lead to embolization to the lungs.

Gouley[33a, b] was of the belief that the long-term result of pulmonary involvement with pneumonia was the

etiologic factor in pulmonary fibrosis and right heart strain seen in the older rheumatic patient. Moscheowitz,[66] however, did not mention rheumatic pneumonia or fibrosis secondary to rheumatic involvement of the lung as a cause of pulmonary hypertension, but he wrote this several years before Gouley advanced his concept.

DIFFERENTIAL DIAGNOSIS

In the foregoing section, several complications of the rheumatic state which might lead to pulmonary manifestations are mentioned. These conditions must be considered in acute rheumatism with abnormal findings in the pulmonary structures. There are several diseases, however, which are quite distinct from rheumatic fever, but which could be confused with rheumatic pneumonia, or, conversely, may be rheumatic pneumonia but are diagnosed as another disease.

Caffey[11] wrote that rheumatic pneumonia should be chiefly distinguished from cardiac failure and bacterial pneumonia. Griffith[38] stressed the confusion possible with other pneumonias, either bacterial or viral. Lees[59] probably had the most complete list of conditions which must be considered when one is confronted with a patient with acute polyarthritis and pulmonary manifestations. His list included: (1) bronchial carcinoma, (2) pulmonary tuberculosis, (3) bacterial pneumonia, (4) bronchiectasis, (5) viral and rickettsial diseases, (6) coccidioidomycosis, (7) subphrenic abscess, (8) asthma, (9) angioneurotic edema, (10) periarteritis (polyarteritis) nodosa, (11) Löffler's pneumonia.

Seldin[90] presented a chart to show the differential between the two most frequent diseases resembling rheumatic pneumonia.

Kneeland and Smetana[50] in 1940 reported 52 cases of bronchopneumonia of unusual character and unknown etiology. There were cases with other manifestations such as migratory polyarthritis, skin rashes, hematuria, fibrinous pericarditis, and encephalitis, any of which might have been cases of rheumatic fever of a bizarre character. Only one such patient died and the descriptions of the organs were entirely commensurate with a diagnosis of rheumatic pneumonia.

DIFFERENTIAL DIAGNOSIS BETWEEN ACUTE PULMONARY EDEMA, RHEUMATIC PNEUMONIA, AND BACTERIAL PNEUMONIA*

SYMPTOMS	ACUTE PULMONARY EDEMA	RHEUMATIC PNEUMONIA	BACTERIAL PNEUMONIA
Active carditis	Not necessary	Always	Rare
Fever	Plus or minus	High	High
Pleurisy	Absent	Frequent	Frequent
Dyspnea	Profound	Profound	Depends on pulmonary signs
Sputum	Pink, frothy	Mucoid, blood streaked	Purulent
Physical signs	Marked	Few	Moderate to marked
X-ray			
Distribution	Nonsegmental	Nonsegmental	Segmental, lobar
Lobes	Multiple, bilateral	Multiple, bilateral	Rarely more than 2 to 3
Type	Soft, hazy, patchy	Soft, hazy, patchy, linear, reticular	Dense, homogeneous
Pathogens in sputum	None	Usually none	Present

*From Seldin, Kaplan, and Bunting.[90]

Atypical virus pneumonia is another disease which might be confused with, or diagnosed instead of, rheumatic pneumonia. Anderson[1] stated that the microscopic picture of rheumatic pneumonia resembles virus pneumonia. Finkelstein and Klainer[25] reported 3 cases of virus pneumonia with pericarditis and all patients recovered. They attributed the pericarditis to the virus of pneumonia. They mentioned the possibility of rheumatic pneumonia but hesitated to diagnose that disease because their cases were mild, the pneumonia persisted (they thought of rheumatic pneumonia as transient), no murmurs were heard, and the electrocardiograms were not typical of rheumatic fever. None of these reasons is valid for excluding rheumatic pneumonia. Jensen[47] believed that many cases of atypical virus pneumonia were really cases of missed rheumatic pneumonia. He reported a case with hemorrhagic nephritis, arthritis, pneumonitis, without cardiac involvement. He stressed the accompanying rheumatic manifestations in rheumatic pneumonia and the value of the antistreptolysin titer in that disease, and that the cold agglutinins should be elevated in virus pneumonia. McKinlay[64] reported 2 cases (with one death) of atypical pneumonia with rheumatic endocarditis. He discussed the possibility that this might have been rheumatic pneumonia, but did not believe the process was a specific one.

Pulmonary congestion from chronic valvular disease is easily confused with other pulmonary manifestations, and must be considered seriously in the older rheumatic patient. Anderson[1] mentioned the possibility of confusion between rheumatic pneumonia and the congestion secondary to mitral disease.

Clark and Kaplan[16] described the changes in tissues associated with serum disease in man. The diffuse arteritis of that condition leads to many manifestations which might cause confusion with rheumatic pneumonia, e.g., arthritis, fever, pneumonitis, skin rashes.

Vascular allergy in the pathogenesis of asthma was discussed by Harkavy,[42] who reported 8 cases of asthma with migratory inflammatory, interstitial lesions of the lungs. In 6 there were pleural effusions; in 3, pericardial involvement also. The electrocardiogram was abnormal in 6 of the 8. Such cases could easily be confused with cases of rheumatic pneumonia. Cole and Korns[18] reported a case which presented many manifestations of angioneurotic edema. There was no autopsy, but rheumatic fever, Löffler's pneumonia, and polyarteritis nodosa were not ruled out in this bizarre case. At various times the patient had edema of the hands, forearms, feet, and face; dyspnea; tachypnea; pulmonary edema; pulmonary infiltration; fever; headache; lymphadenopathy; and vague skin rashes but no joint symptoms. There was an eosinophilia of 50 to 80 per cent. Vaughan and Hawke[100] reported upon a man with angioneurotic edema who suffered from repeated and extremely varied symptoms attributed to allergy. Among these symptoms were meningismus, headache, hydrarthrosis, symptoms of appendicitis, sinusitis, pulmonary edema, and pulmonary infiltration resembling miliary tuberculosis which cleared after an Adrenalin injection.

Elkeles[22] reported a case with changing roentgen-ray manifestations in the lungs, fever, arthritis, eosinophilia, and

neurologic changes. Clinically the author did not rule out rheumatic fever, Löffler's pneumonia, or angioneurotic edema. At autopsy, however, the patient was found to have polyarteritis nodosa. Friedberg and Gross[28] reported 8 cases of polyarteritis nodosa in 4 of which there was evidence of rheumatic heart disease by the presence of Aschoff nodules in the myocardium. They suggested that rheumatic fever might be a cause of polyarteritis nodosa. Pneumonia was not discussed. It might be more reasonable to say that rheumatic fever probably resembles polyarteritis clinically and pathologically. Weir[103] reported a case with asthma, skin rash, cardiac disease, renal disease and eosinophilia as a case of polyarteritis nodosa. The descriptions of the roentgen-ray findings resembled those reported in rheumatic pneumonia: "The hilar shadows are increased in width with marked increase in the lung markings, particularly in the hilar regions and lower lung fields."

Woodland[106] reported a case of a 16-year-old boy with rheumatism, pulmonary opacity, increased sedimentation rate, pericardial friction rub, tic-tac cardiac action, pleural rub and effusion, which, after six negative examinations for acid-fast organisms, was finally diagnosed as tuberculous rheumatism. In general tuberculosis should not be confused with rheumatic pneumonia. Neubuerger and associates[71] cited one proved case of rheumatic pneumonia which had the distinctive roentgen picture of miliary tuberculosis.

LABORATORY AND ROENTGENOGRAM

Other than the laboratory findings of acute rheumatic fever, rheumatic pneumonia presents no special laboratory features. As in acute rheumatic arthritis, carditis, etc., one might expect to find an elevation in the total white-cell count, with a preponderance of polymorphonuclear cells. There is often an anemia of mild degree, the cause of which is not understood. Platelets and other cellular elements are normal. The erythrocyte sedimentation rate is almost always elevated. If more complicated procedures are available, it may be found that the antistreptolysin, and the antihyaluronidase titers are elevated, just as in the simpler cases of acute rheumatic fever.

Changes in the cellular elements of the urine may be encountered, red blood cells being present in the sediment, and there may be proteinuria. These urinary changes probably reflect the generalized vascular involvement in severe rheumatism. The urinary changes are found more frequently in severe cases with pericarditis, pneumonia, myocarditis, than in the less severe cases of acute rheumatism.

The electrocardiogram may be abnormal, just as in other rheumatic patients. Lustock,[58] in reporting 12 necropsy-proved cases of rheumatic pneumonia, stated that the ECG evidence of progression was invariably present.

In recent decades, since the virus or bacterial etiology of rheumatic fever is no longer widely held, all authors agree that there are no consistent bacteriologic findings in rheumatic pneumonia. Neubuerger[71] studied 8 distinctive cases at autopsy with negative bacteriologic studies of the lungs. Bacteriologic studies have been attempted and reported repeatedly by many authors,[62, 72, 75b, 90, 109] all with

negative results. Studies of the pleural fluid for organisms directly or on culture have been negative.[79, 87]

Sabrazes (according to Paul[75b]) did cell counts of the pleural fluid of patients with acute rheumatism without arriving at any definite conclusions. He reported finding endothelial cells with polymorphonuclear cells during the acute disease.

Perhaps the most helpful clinical examination is the roentgenogram of the chest. Caffey[11] characterized the chest roentgenogram as "fleeting and migratory" and said that many lobes may be simultaneously involved. Gouley[33a] warned that often the roentgenograms were interpreted as "passive congestion." Griffith[38] pointed out the patchy, shifting nature and mentioned the resemblance to pulmonary infarction. Pleurisy may also be seen. Levy[56] stressed the fleeting character. Lustock[58] described many roentgenographic findings in cases coming to autopsy: consolidation, hilar engorgement, edema, peribronchial nodules. He pointed out, as have others, that the roentgen-ray findings did not parallel the clinical course or findings. Neubuerger,[71] on the other hand, minimized the value of the roentgen ray. He found only one case in 8 that had roentgenograms of diagnostic value. One of his patients had chest films which resembled those in miliary tuberculosis. Rantz[82] described 3 cases of "poststreptococcal" pneumonia diagnosed by roentgen ray. In one of these cases the roentgenogram was normal on the day that chest symptoms were prominent; the roentgen-ray changes in the lungs appeared later. Reimann[84] mentioned the patchy, transient, shifting nature of the roentgen-ray findings, as well as the possibility of lobar consolidation, atelectasis, and pleural fluid.

Schwedel[89] gave a complete discussion of the roentgen-ray findings in rheumatic fever. These include: pulmonary congestion, either vascular or interstitial; pleural effusion; infarction; acute pulmonary edema; chronic pulmonary edema; pneumonia; fibrosis; and pleural thickening. Seldin[90] and Schwedel[89] both stressed the "butterfly" distribution of the infiltration about the hilar regions with a peripheral clear zone. Weir[103] described similar findings in polyarteritis nodosa. Woodland[106] described roentgen-ray findings in the lungs resembling infarction, later going on to pleural effusion and lobar consolidation in a case of tuberculous rheumatism.

PROGNOSIS

The prognosis of the patient who develops rheumatic pneumonia is difficult to determine. As in other diseases, one may predict on the basis of the findings in the individual case, complemented by what is known of the over-all experience in a large number of clinical cases. It is interesting to note the statements of various authors as to their experience regarding prognosis.

Rabinowitz[81] stated that rheumatic pneumonia was a "pneumopathy of fleeting character which did not influence prognosis," and which "rarely causes death." One of the earliest writers to describe pneumonitis was Naish[70] who stated in 1928 that the pulmonary features "do not usually appear to add much to the gravity of the prognosis, and the great majority live for the dullness to clear up." In 1950 Lustock[58] stated that the manifestations of pneumonitis did not produce a syndrome which was uniformly fatal

and that frequently the "complication" was not recognized until autopsy.

The authors who had little fear of pneumonia in rheumatic fever are in the minority, and most writers dreaded this manifestation. Latham[52] in 1845 said that "such forms of pulmonary inflammation are portentous ingredients in the clinical history of acute rheumatism, and give a fearful interest to it." Ormerod[73] in 1858 wrote that the pneumonia usually was a prominent feature in the cause of death in acute rheumatism. He thought therapy was useless. Fuller[29] in 1864 wrote that "its appearance is fraught with unusual danger." He stressed that in almost all fatal cases of carditis one would also find pleurisy or pneumonia or both present. Pye-Smith[80] in 1873 thought of the pneumonia as an accidental complication rather than a fundamental part of the rheumatic state, but he thought it was one of the "most frequent causes of death." Garrod[31] in 1890 thought that in milder cases the prognosis was no worse than that usual in rheumatism, but stressed the hazard of extensive, "especially double pneumonia." Griffith[37] in 1947 wrote that pneumonia was second to carditis in importance because of its frequency, its relationship to right-sided heart failure, and because it was an important cause of death. Seldin[90] thought the prognosis very grave because all 6 of his reported cases were fatal.

Gouley[33a] formulated the concept that the prognosis might be unfavorable in other ways than by increasing the death rate in acute rheumatism; that is, he wrote, that rheumatic pneumonia might be the cause of chronic, fibrotic changes in the lung which eventually would lead to right-heart strain and thus to a chronic complication of the rheumatic syndrome. Reimann[84] in 1954 wrote that the pneumonia might lead to chronic fibrotic changes in the lungs, resulting in protracted cardiac difficulties.

It may be said that the prognosis of rheumatic pneumonia is not clearly known, but that probably it is not always fatal. With more thorough search for rheumatic pneumonia and with improved therapy, many more cases of this disease may be seen which do not terminate in death.

TREATMENT

Antibiotic and chemotherapeutic agents have not proved to have any specific effect on the pulmonary manifestations of the rheumatic syndrome. This is not to say that these agents may be omitted, primarily because of the difficulty of distinguishing between bacterial and rheumatic pneumonia, but also because the pneumonic lungs are vulnerable to secondary bacterial invasion. Levy[56] in 1948 reported 6 cases, 2 treated with sulfadiazine without response, and 2 treated with penicillin without improvement. He noted no response in 5 cases with salicylate therapy. Benadryl was tried in one case without benefit. The conclusions were that there was no specific therapy for rheumatic pneumonitis. Neubuerger[71] in 1944, and Nittono and Hoshiyama[72] in 1940 reported no success with sulfonamide drugs in rheumatic pneumonia. Seldin[90] in 1947 had no favorable response to penicillin given intravenously in this condition.

Benoist[5] in 1900 said the response to salicylates in rheumatic pneumonia was prompt and might be diagnostic. Fischel[26] in 1952 stated that pleuritis once occurred during salicylate therapy in one of their cases, but they stated

that salicylates may affect rheumatic inflammation of the "extra-articular serosal membranes." Gamna[30] wrote of clinical cases which responded to salicylates. Goyena[35] wrote that the response of the pulmonary manifestations was prompt.

On the other hand, Caussade and Tordieu[12] said that the salicylates had no effect on the pulmonary or pleural lesions. Grenet[36] stated that the salicylates were not effective in pulmonary or pleural manifestations. Myers and Ferris[69] stated that the salicylates not only did not help, but that the pleural manifestations interfered with the usual salutary effect they had on joint symptoms. Naish[70] wrote that salicylates did little except keep the fever down; Reimann[84] that the salicylates may relieve the discomfort in rheumatic pneumonia. Seldin, Kaplan, and Bunting[90] obtained no response to salicylates, digitalis, or intravenous penicillin. Sokolow and Snell[92] described a patient who had pneumonia, pericarditis, and pleurisy, treated with salicylates, in whom the fever persisted for 13 days of treatment.

Stewart[94] wrote that salicylates were effective against pericardial effusion, but did not mention pneumonia.

Reimann,[84] writing in 1954, stated that rheumatic pneumonia "no doubt will respond to therapy with cortisone and ACTH as other rheumatic manifestations do." The interesting possibilities suggested by these agents have been and are being investigated, but there are few published accounts of their use in rheumatic pneumonia. Chancey[13] in 1953 reported 2 cases of rheumatic pneumonia treated with intravenous ACTH which he considered lifesaving. In each case, however, the pneumonitis developed while the patients were receiving 300 mg. of cortisone daily. In neither case was there residual cardiac damage. The prompt clearing and the lack of cardiac findings make the diagnosis of rheumatic pneumonia open to some question. Shopfner and Seife[91] in 1952 reported a case of rheumatic pneumonia which occurred as a rebound phenomenon after small doses (50 mg. per day) of ACTH were discontinued. Their patient died in a few hours, and rheumatic pneumonia was confirmed at autopsy. Lustock and Kuzma[116] in 1956 also reported on the failure of ACTH in one of the patients in their series.

No other reports of cases treated with these hormones have been found. Dorfman,[21] Massell,[61a, b] Robinson,[86] Fischel,[26] Bunim,[108] Rowe,[109] Wilson,[110] Harris,[111] Markowitz,[112] Houser,[113] Taran,[114] and Barnes[115] have all written on the subject of ACTH and cortisone in rheumatic fever, but did not report cases of pneumonia treated with these agents.

SUMMARY

1. Involvement of the lungs by the rheumatic process has been recognized and described for many years, as far back as the late eighteenth century.

2. There are no reliable figures on the frequency which this manifestation is seen in rheumatic fever. The available data show a range of 2 per cent to as high as 60 per cent.

3. The etiology and pathogenesis are imperfectly understood. The most likely considerations are that: (a) The pneumonia is part of the rheumatic process. (b) The pneumonia is secondary to the cardiac lesion or cardiac failure. (c) Intercurrent infection is

the basis for the pneumonia. (d) The pneumonia is a combination of a and b.

4. The clinical picture of this syndrome is not specific, so that the diagnosis is difficult to make ante mortem but it may be suspected. The diagnosis can be made with certainty only by gross post-mortem and microscopic examination of the heart and lungs.

5. Laboratory procedures offer little in establishing a definite diagnosis of rheumatic pneumonitis. The findings by roentgen ray may be suggestive, but not diagnostic. The evidence of pneumonitis is usually a patchy, migratory, and persistent type of infiltration.

6. In considering the differential diagnosis, one must consider active carditis, acute pulmonary edema, bacterial and viral pneumonia, and pulmonary congestion caused by chronic valvar disease.

7. The prognosis is very grave since rheumatic pneumonitis seems to occur in individuals who have associated severe involvement of the heart.

8. The results of treatment are difficult to evaluate because it is difficult to make the diagnosis ante mortem. Little is known about the effect of hormone therapy upon rheumatic pneumonia.

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Comments on Current Literature

CONGENITAL DAMAGE TO THE CENTRAL NERVOUS SYSTEM AS A RESULT OF INTRAUTERINE INFECTION

ONLY within comparatively recent years has fetal infection been recognized as a primary cause of central nervous system disease in the newborn infant, intrauterine infection having been considered of relatively rare occurrence in the past. On the basis of extensive survey studies at the Chicago Lying-in Hospital from 1939 to 1943, Potter and Adair[1] concluded that "infections are not common in this period (early neonatal), and the few which are found consist almost entirely of pneumonia." In one series of 2,000 consecutive fetal or neonatal deaths reported in 1940, Potter[2] found infection other than syphilis in only about 8 per cent. All of these infections were classified as pneumonia on the basis either of gross or of microscopic study. Within the past decade, however, evidence has accumulated which would place intrauterine infection in a more important position as a cause of meningitis or encephalitis in the newly born infant and as a source of changes capable of disturbing the normal course of central nervous system development.

Among the types of fetal infection reported, toxoplasmosis and some infections of viral etiology have been prominent. Toxoplasmosis, a protozoan infection, produces severe damage in the central nervous system of the human fetus, yet the mother may show no overt signs of disease. The same situation may obtain in viral infections which are subclinical or completely silent. With increasing knowledge concerning the behavior of viruses and their tendency toward systemic spread, possible placental transfer of such agents assumes a new significance. As early as 1943, Medovy[3] cited two examples of encephalitis occurring in newborn infants during a sizable outbreak (509 recognized cases) of Western equine encephalomyelitis in Manitoba. Onset of illness in these two newborn infants was on the third and fourth days of life, respectively, while they were still in the maternity hospital nursery. In each instance the mother had experienced a recent febrile illness and showed laboratory evidence of Western equine encephalomyelitis. Both infants developed significant antibody titers against the Western equine virus. Subsequently both showed evidence of residual damage and were admitted to the Children's Hospital at Winnipeg for evaluation because of spasticity, slow development, and apparent mental retardation. Two cases of Western equine encephalomyelitis in newborn infants were encountered in recent epidemics in the western part

of the United States (1956-1957). Moderately severe clinical manifestations were apparent soon after birth, and the infection was considered congenital. At the present time these infants are being followed closely for the development of sequelae.

Congenital damage to the central nervous system in animals as a result of virus infection in the mother is well recognized by husbandmen and veterinarians, both in natural infections and in immunization procedures. Immunization of pregnant swine with living attenuated hog cholera vaccine is contraindicated for this reason.[4] Hog cholera virus attenuated by rabbit passage until it has lost all capacity to induce significant symptoms in swine, constitutes an excellent immunizing agent which has been used extensively in this field. However, when sows are inoculated in the first thirty days of pregnancy, gross fetal damage results. One-third to one-half the young may be stillborn, and the remainder show marked congenital malformations. Active virus can be recovered readily from fetal spleen and from other tissues. Similar damage to the fetus has been reported following the vaccination of sheep against catarrhal fever (blue tongue virus) within the period covering the first two months of pregnancy. Stillbirths studied for pathogenesis showed brain malformation and a condition resembling internal hydrocephalus. Surviving young may be retarded in growth and development, may be blind or dumb.[5] Similarly, during epizootics of Japanese B encephalitis in swine, large numbers of stillbirths and abnormal offspring have been recorded.[6] Serum surveys among swine in one such epidemic area suggested a high incidence of inapparent infection with the virus of Japanese B encephalitis. Pregnant females, apparently normal, gave birth to their young at or near the expected date of delivery. In some instances all the young in the litter were dead; in other instances, live, dead, and moribund piglets were observed in the same litter. Those alive were observed to be weak and unable to stand or to nurse. Some young, which appeared normal at birth, later developed signs of central nervous system involvement. Necropsy findings on a number of the latter group included encephalomalacia, hydranencephaly, and changes in the cerebral blood vessels. The virus of Japanese B encephalitis was isolated from brain tissue in the case of three of these piglets.

An interesting and informative review by Potter,[7] which concerns placental transfer of viruses in human subjects, appeared in the *American Journal of Obstetrics and Gynecology* for September, 1957. Presented at a meeting of the Chicago Gynecological Society, this report summarizes the present-day position with respect to placental transmission and has special reference to the "intrauterine origin of cytomegalic inclusion body disease." The author stresses the fact that human salivary gland virus, rarely responsible for overt illness in the mother, may cause severe damage or fatal disease when transferred placentally to the fetus. "Whenever a child is born with symptoms of severe erythroblastosis, the possibility that these may be caused by salivary gland virus, and not by maternal isoimmunization must be considered. This is especially true if the mother is Rh positive." The pathogenesis of the

disease varies according to age at the time of infection. When manifestations are noted at birth, infection has probably occurred early in intrauterine life; typical findings of the disease at birth include splenomegaly and hepatomegaly, erythroblastemia and anemia. Jaundice appears within a few hours after birth, blood destruction with compensatory erythropoiesis being marked in this congenital form. At necropsy, extensive ectopic erythropoiesis is apparent, and in many viscera greatly enlarged cells are seen which contain intranuclear and intracytoplasmic inclusions. When the disease has been acquired in utero, these cytomegalic inclusions are more prominent in the kidney than in other organs. Potter points out that both in newborn infants and in older infants and children, examination of the urinary sediment is rewarding as a diagnostic procedure, since typical desquamated renal tubule cells containing intranuclear, or intracytoplasmic inclusions, or both, will be seen in the urine. If the infection is acquired in infancy, symptoms referable to the respiratory tract or the intestinal tract are prominent, with inclusion bodies found most abundantly in the lungs. While in older children and adults the infection seems to be localized in the salivary glands, which show numerous inclusions, actually the virus is widespread in the body—in the liver, kidney, and other organs.

Potter refers to the work of Smith[8] on salivary gland disease: recognition of the disease, its pathogenesis in mice, propagation of the viruses of mouse and human salivary gland disease in tissue culture. "With the report by Margaret Smith in April, 1956, of the successful propagation of human salivary gland virus in tissue culture, the last doubt was dispelled that these inclusions in the human are caused by a virus which, like salivary gland viruses found in other animals, is species specific."[7] Potter refers also to the work of Weller and his associates[9] concerning the isolation of strains of salivary gland virus from living children with signs and symptoms of cytomegalic inclusion disease: isolation of virus in one patient from liver biopsy tissue taken at the age of 3 months; in a second patient from liver biopsy tissue and from urine specimens taken on three occasions. In a third child who had been ill since birth, typical cytomegalic cells with inclusions had been observed repeatedly in the urinary sediment, and the virus was isolated from urine for a period of ninety-one days. This persistent viruria may be of considerable significance.[9] When cerebral calcification is present in inclusion body disease, the condition must be differentiated from congenital toxoplasmosis. Calcification in inclusion body disease, however, occurs largely in the subependymal regions of the lateral ventricles, associated with dilatation of the ventricles and poor development of the convolutions. In toxoplasmosis, the calcification shows a more variable distribution and is of later appearance. In both types of infection destructive action of the organisms may be restricted to a limited area of the brain, the electroencephalogram may be entirely normal, and the objective signs of retardation transient and difficult to evaluate.[10] While the salivary gland virus does have a definite predilection for brain tissue, the degree

of invasion and destruction varies, with resultant variability in the sequelae. Some fetuses seem to be more susceptible than others; some escape infection entirely. Potter points out that subsequent birth of a normal infant is possible, either because of fetal resistance or because the virus no longer passes the placental barrier.

While bacterial meningitis with attendant central nervous system damage in early neonatal life does not appear to be of common occurrence, a number of instances have been recorded in which infection of the meninges was thought to be of antenatal origin. These recorded cases include intrauterine and neonatal otitis with otitic meningitis,[11] antepartum gas bacillus infection with loss of the fetus in a mother with septicemia,[12] transplacental infection with hemolytic streptococcus,[13] intrauterine infection with *Leptospira icterohaemorrhagicae*,[14] etc. An interesting case was described in 1951 by Crosby, Mosberg, and Smith[15] under the title, "Intrauterine Meningitis as a Cause of Hydrocephalus." This case was that of a female infant who was admitted to the hospital at 3 days of age because of an enlarged head evident even before birth. The enlarged head had been suspected during the seventh month of pregnancy, and, at the time of the eighth-month routine examination, x-ray studies verified this impression of hydrocephalus. After six weeks of unsatisfactory treatment, surgical intervention was attempted. Exploration of the meninges showed the presence of a yellow organizing exudate from which a pure culture of *Staphylococcus aureus hemolyticus* was obtained. Investigation into the mother's history revealed intermittent upper respiratory infections throughout the entire pregnancy. During the third month, impacted molar teeth had been removed with prompt healing of the sockets and no apparent ill effects. There was no question in this case of premature rupture of the membranes, and the authors concluded that the "probable mode of infection in this infant was by a transient blood stream infection in the mother with transplacental transmission . . . between the sixth and seventh months." The child was followed closely for about one year when the head and chest both measured 52 cm. in circumference; the anterior fontanel was still open at this time, and moderately tense; the coronal suture was readily palpable and slightly separated. Follow-up beyond one year was not possible.

Fungus infection of the vagina during pregnancy is a frequent complication. Usually there is no untoward effect on the course of the pregnancy or on the development of the fetus. Under certain circumstances, however, severe damage of the developing central nervous system is possible. Three newborn infants with diffuse fungus infection *(Cryptococcus neoformans)* were described in 1948 by Neuhauser and Tucker.[16] Each of these patients showed clinical evidence of hydrocephalus and, on roentgenographic examination, "confluent calcification of the severely degenerated brain." The infections were "evidently acquired in utero, during delivery, or very early in the neonatal period. The damage produced by the fungus was severe, and in these three patients

fatal within the first few weeks after birth."[16] Two recent case reports, one in the British and one in the American literature, likewise call attention to the potential fetal hazards associated with fungus infection in the mother. The April, 1957, issue of the *Archives of Disease in Childhood* carried a brief but careful study by Burry[17] of Christ Church, New Zealand, reporting a case of hydrocephalus associated with intrauterine fungal infection. The infant, a male with birth weight of 7½ pounds, was born at term after a "short forceful labor" of two hours' duration. Conception had followed closely after dilatation and curettage and tubal insufflation, carried out because of apparent infertility. The infant was slow to breathe and cry, but responded well to oxygen and incubation. Soon after birth it was noted that the child's sucking and swallowing reflexes were poor, and for the first fortnight tube feeding was required. Twitching of the eyelids and face began on the third day of life; on the fifth day, undue separation of the skull sutures was apparent, and the diagnosis of hydrocephalus was suggested. Under constant care this child survived for thirty-seven days. Postmortem examination revealed gross hydrocephalus involving the lateral and third ventricles; the cerebral hemispheres were tense and distended with marked flattening of the sulci; a pale organized exudate covered the occipital poles. Sections from the lining of the lateral ventricles showed loss of much of the ependymal layer, the cells of remaining portions being flattened to cuboidal form. "Beneath a layer of glial scarring, and at some points penetrating more deeply into the brain substance, were irregular masses of partly calcified necrotic material and structures identifiable by P.A.S. stains as hyphae and spores of a fungus." Unfortunately no cultures were attempted; however, the presence of septate pseudomycelia and small spores suggested *Candida albicans* as the most likely pathogen. The grave condition of this infant at birth and the subsequent pathologic findings led the author to the conclusion that this infection was intrauterine in origin. The second case report, which appeared in the *American Journal of Obstetrics and Gynecology* for January, 1958, describes *Candida albicans* infection of the amniotic sac. This report is believed by the authors, Benirschke and Raphael,[18] to be the first recorded instance of *Candida albicans* infection of the umbilical cord. The mother, gravida ii, para i, was in the second month of pregnancy when first seen by her obstetrician. She was complaining of vaginal irritation for which she had been employing self-medication. Following proper treatment this condition improved, and the months following were uneventful. In the sixth month, however, premature labor began, and a female anencephalic infant was delivered by breech presentation. This child lived for about forty minutes after birth; autopsy was not performed. The placenta, cord, and membranes were studied in detail; the fetal surface of the placenta showed severe chorioamnionitis. The amniotic epithelium had degenerated almost completely, and the underlying connective tissue of the amnion and chorion was infiltrated with

acute inflammatory cells. Walls of the fetal blood vessels were damaged, and sections of the umbilical cord revealed acute inflammatory cells (fetal) in the walls of the umbilical vessels and in the cord substance. Large colonies of fungus growth were present on the surface of the cord. Widespread distribution of the fungus was apparent on staining with P.A.S. stain. From the surface of the cord and amnion *Candida albicans* was isolated in pure culture. Since there was no history of premature rupture of the membranes, the authors suggest that an early subclinical rupture of the membranes with subsequent sealing of the rupture site might have occurred during active moniliasis in the mother. The condition of the child at birth and the extent of involvement of the cord and membranes suggested that the infection was of considerable duration.

Such infectious agents transferred from the mother to the fetus may bring about their effects either directly on the fetal tissues or indirectly by altering the general fetal milieu. Some of these agents seem to have an affinity for the blood vessels, particularly the arteries of the cerebral circulation. In developing chick embryos artificial partial occlusion of major cerebral vessels has been shown to result in disturbance of differentiative processes and in retardation of the subsequent development of the brain. The association of vascular anomalies with anencephaly in the human fetus, in the absence of known infection, is being studied currently by pathologists.[19] Composite information accumulating from all sources will help to further a basic understanding of the disturbances in fetal life which interfere with the normal course of central nervous system development.

RUSSELL J. BLATTNER

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News and Notes

The National Association for the Prevention of Tuberculosis will hold a Commonwealth Chest Conference in London, July 1 to 4. Representatives from thirty-five different countries are expected to attend. Further information as to the program, etc., may be obtained from the National Association, Tavistock House North, Tavistock Square, London, W.C. 1, England.

Among the twenty-five scholars in medical science recently appointed by the **Markle Foundation**, two in the field of pediatrics are included: Donough O'Brien, of the University of Colorado School of Medicine; and Ned W. Smull, instructor at the University of Kansas School of Medicine in Kansas City.

The **Cook County Graduate School of Medicine** announces a two-week intensive course in Neuromuscular Diseases of Children with special emphasis on cerebral palsy, to be given by Dr. Meyer A. Perlstein for the period of July 7 to 18. This is an intensive didactic and clinical course designed for pediatricians, orthopedists, neurologists, psychiatrists, and physiatrists interested in the care and treatment of children with neuromuscular handicaps. Emphasis will be placed on the practical clinical aspects of treatment and rehabilitation procedures. The course will include trips to demonstration clinics and treatment centers. Registration is limited. For further information, write to John W. Neal, Registrar, Cook County Graduate School of Medicine, 707 S. Wood Street, Chicago, Ill.

The **Tenth Annual Summer Clinics of The Children's Hospital in Denver, Colo.**, will be held June 18, 19, and 20, 1958. Designed for all physicians concerned with the care of infants and children, the course will present recent advances in medical knowledge appropriate to practice and will emphasize early recognition of disease and common problems in the management of children's diseases, and will outline successful programs of therapy.

Guest faculty this year will be Dr. Lee Forrest Hill, Chief of Staff, Raymond Blank Memorial Hospital, Des Moines; Dr. Meyer A. Perlstein, Professor of Pediatrics, Cook County Hospital, Chicago; and Dr. William B. Kiesewetter, Surgeon in Chief, Children's Hospital of Pittsburgh.

Further information can be secured by writing the Chairman, Summer Clinics Committee, Children's Hospital, Denver 18, Colo.

Childrens Hospital, Columbus, Ohio, affiliated with the Ohio State University College of Medicine, offers a one-year residency in pediatric allergy to candidates with two years accredited residency in pediatrics. Address correspondence to John H. Mitchell, M.D., Division of Allergy, Ohio State University, Columbus, Ohio.

The Editors of *Modern Medical Monographs*, a quarterly publication, announce an award for the best unpublished manuscript for a short book on a clinical subject in the field of internal medicine. The purpose of this award, which will be known as the **Modern Medical Monograph Award**, is to stimulate young physicians to communicate their work in the classical form of the monograph and to achieve high standards of medical writing. The winner of this competition will receive five hundred dollars. In addition, the winning monograph, if found suitable, will be published as a book in the series *Modern Medical*

Monographs. The generosity and cooperation of Dr. Henry M. Stratton, President of Grune & Stratton, Inc., publishers of the series, have made this award possible.

The entries will be judged for style and clarity of expression by a committee of the American Medical Writers' Association and for clinical interest and scientific value by the Editors and Advisory Board of *Modern Medical Monographs.*

The rules are as follows:

1. The author (or authors) must be a graduate physician, less than 40 years of age. Single authorship is preferred, but two co-authors will be acceptable. The name of the medical school from which the author graduated and his date of graduation should be stated.

2. Manuscripts should be submitted in duplicate (original and one copy) by registered mail, postmarked *no later than Oct. 1, 1958,* to Richard H. Orr, M.D., 37 East 67th St., New York 21, N. Y.

3. The manuscript, including the bibliography, must consist of between 115 and 200 double-spaced typewritten pages with ample margins and not more than 40 illustrations (figures or photographs). For each illustration used, the allowable upper limit of typewritten manuscript pages should be reduced by one.

4. Fishbein's book, *Medical Writing* (third edition), should be followed in preparation of the manuscript, use of abbreviations, and bibliographic form.

Richard H. Orr, M.D. Consulting Editor

Irving S. Wright, M.D. Editor-in-Chief

The **University of Nebraska College of Medicine** offers a postgraduate course, Allergy Conference, May 8 and 9, 1958. May 8 will be given to Pediatric Allergy, followed in the evening by a dinner with the Nebraska Pediatric Society, at which there will be a panel discussion on the "Use and Abuse of Drugs in the Treatment of Allergy." Details may be obtained from Dr. Lawrence A. Cappiello, Supervisor of Medical Extension, University of Nebraska Medical School, Omaha 5, Neb.

A **Postgraduate Seminar in Pediatrics** will be conducted by the combined faculties of the Georgetown and George Washington Departments of Pediatrics at the Children's Hospital of Washington, D. C., on May 22, 23, and 24, 1958. The program will be given by members of the two teaching institutions and guests from The National Institutes of Health, The Walter Reed Army Medical Center, and The Bethesda Naval Hospital.

Further information may be obtained from The Director of Medical Education, Children's Hospital of Washington, D. C., 2125 Thirteenth Street, N.W., Washington 9, D. C.

The **XI Polish Pediatric Congress** will be held on June 6, 7, and 8, 1958, in Wroclaw. The main problems of the Congress are: (1) meningitis in children (excluding tuberculous meningitis), (2) staphylococcal infections in children.

Books

Sins of Their Fathers. Marjorie Rittwagen, M.D., Boston, 1958, Houghton Mifflin Co., 264 pages. Price $3.50.

Juvenile delinquency—the theme of this book—is a subject of much concern. Seemingly a rapid increase is taking place, and our newspapers in recent months have been filled with lurid accounts of "teenage" gangsterism and of delinquents involved in murder, rape, robbery, and vandalism. It is a national problem not confined to any one city or section. While fundamentally a social, and to some extent a psychiatric, problem, it is a matter of interest to the pediatrician who is so deeply concerned with all aspects of the welfare of children. It is for this reason that this book by Dr. Rittwagen, Staff Psychiatrist to the Court of Domestic Relations of the City of New York, is of unusual interest. It covers the subject in a broad way, and her experiences with and observation of delinquent children over a five-year period is presented in an interesting and readable way. The title of the book indicates the author's general conclusions as to the chief or fundamental causes of juvenile delinquency. The delinquent child comes usually from a home that is broken or unwholesome, as a result of psychotic, alcoholic, immoral, or mentally retarded parents. As a result of the home situation, the child is deserted or neglected or abused, and deprived of the normal emotional needs of the young child. There are many factors involved which are often combined as regards the specific child. One of these is the density of the child population in an area in relation to the schools and recreational facilities available. In this connection is the interesting observation that the juvenile delinquency rate is increasing in the modern new housing projects being built in many cities to replace the run-down slum areas. The author's approach is by a limited case history record upon which the general discussion of the particular point or subject is developed, and in this way the many facets of the problem are skillfully presented. Much of the discussion is concerned with the work of the governmental and private agencies that are trying to cope with the problem, such as the courts and detention homes, the hospital and psychiatric clinics, the welfare and religious organizations. These are woefully inadequate compared with the magnitude of the problem.

It is a sordid and distressing picture. While fully agreeing with the author that what is needed is adequate personnel and increased facilities of a number of kinds to meet the present urgent problem, increase in the psychiatric facilities, for example, will not reach the basic problem of removing or correcting the causes of juvenile delinquency. The many-sided factors or influences that lead to juvenile delinquency are well stated in a sentence by the author: "The delinquents I've seen are the products, then, of their genetic inheritance, their parents' influence, their neighborhood, their schools, their church, their time." The book gives an excellent picture of the juvenile delinquent and his personal and community problems. The book is very well written.

B. S. V.

Reaching Delinquents Through Reading. Melvin Roman, Ph.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 125 pages. Price $4.50.

It is generally accepted that a close relationship exists between personality difficulties and reading disabilities. Several studies have shown that about 85 per cent of juvenile delinquents have reading disabilities compared with 10 per cent of all children of school age. Dr. Roman, former Director of Group Psychotherapy of the New York City Court of Domestic Relations, in this monograph discusses the problem and therapy. He considers what is

called "Tutorial Group Therapy" as the method producing the best results. The book is of interest to those working with the juvenile delinquent rather than of general interest.

Urine and the Urinary Sediment. Second Edition. Richard Lippman, M.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 140 pages. Price $8.50.

This book contains an excellent section on the significance and source of protein and the formed elements of the urine. There are 92 colored photographs showing the various types of casts, red and white blood cells, epithelial cells, crystals, yeast, fat, bacteria, etc.

Another section deals with urine and its sediment in various diseases. There is also a brief clinical classification of these diseases.

A third section deals with general considerations of urine (volume, appearance, color, odor, pH) and technical descriptions of timed urine collections, methods of qualitative and quantitative examinations, and descriptions for staining sediment. This book is easily read and contains much valuable information. The excellent colored photographs should make it extremely valuable to the relatively inexperienced observer.

H. W.

A Parents' Guide to Children's Illnesses. John Henderson, M.D., New York, 1957, Duell, Sloan & Pearce, Inc., 398 pages. Price $4.75.

This is another of the many books on children's diseases written for parents. It is the experience of many pediatricians that such books often do more harm than good, in line with the sound adage that a little learning is a dangerous thing. Parental diagnosis can be very dangerous to the child. Dr. Henderson's text, in the opinion of the reviewer, goes into far too many details and would be confusing rather than helpful to most parents. There are eight pages of rather poor colored plates containing twenty-six pictures of rashes and other lesions. Some are rather silly to include in a book for parents, such as pustular lesions on an ankle and part of a leg labeled "smallpox." There are several better books available for parents on children's illnesses which the reviewer would recommend if the necessity arose.

The Infantile Cerebral Palsies. Written by the Little Committee for the Study of the Infantile Cerebral Palsies (Drs. W. R. F. Collis, William Dunham, L. T. Hilliard, David Lawson, and Mrs. Eirene Collis. Foreword by Sir Francis Walshe), Springfield, Ill., 1957, Charles C Thomas, Publisher, 100 pages. Price $3.00.

This short monograph is a very worthwhile addition to the voluminous literature on the subject of the cerebral palsies. The discussion goes back to Little's descriptions and writings in 1853, and emphasis is placed on the "new" approach to cerebral palsy in recent years being simply a return to the views expressed by Little over 100 years ago. The text takes up the diagnosis, types, and management of the condition. This is followed by a discussion of the organization of cerebral palsy services. All members of the Little Committee have been working in the field of cerebral palsy, and their contribution is well worth while. It is a well-written and interesting presentation of the subject. Recommended.

Metabolic Aspects of Transport Across Cell Membranes. Q. R. Murphy, Editor, Madison, Wisconsin, 1957, The University of Wisconsin Press, 379 pages. Price $7.50.

This book includes papers and discussions of a symposium held at the University of Wisconsin under the sponsorship of the University Medical School. With the purpose of summarizing and correlating the large amount of information available on membrane transport, the symposium emphasized problems involving skin, nerve, muscle, gastric and intestinal mucosa, and the kidney. Discussions of fluid exchange and the effect of metabolic derangements on ion exchange in the whole organism were included, and some attention was given to possible correlations of clinical problems and basic information.

A. F. H.

Stedman's Medical Dictionary, ed. 19. Edited by Norman B. Taylor, M.D., F.R.C.S.(Edin.), M.R.C.S.(Lond.), Baltimore, 1957, Williams & Wilkins Co., 1656 pages. Price $12.50.

A new revised edition of Stedman's dictionary. Several thousand new words and terms have been included which have come into use since the last edition four years ago. The names of pharmaceutical preparations have been changed from Latin to English in conformity with the changes in the American and British pharmacopeias.

Aids to Diagnosis and Treatment of Diseases of Children, ed. 10, F. M. B. Allen, M.D., F.R.C.P.(Lond.), Baltimore, 1957, Williams & Wilkins Co., 302 pages. Price 10s. 6d.

A small pocket-sized book in the Students' Aids Series published in England. The pediatric text first appeared in 1893, and, since 1927, has been written by Dr. Allen of the Royal Belfast Hospital for Sick Children. It is more of a miniature text than a synopsis, and from the number of editions has evidently been popular with British medical students. Good of its kind.

Deafness, Mutism and Mental Deficiency in Children. Louis Minski, M.D., New York, 1957, Philosophical Library, Inc., 82 pages. Price $3.75.

In this book Dr. Minski gives an excellent textbook presentation of the subject of deafness and mutism in children. He stresses the importance of differentiating between mentally defective and deaf children and presents a lucid exposition of the techniques of assessing deafness-audiometry, electroencephalography, and psychologic testing.

Manual of Pediatric Physical Diagnosis. Lewis A. Barness, M.D., Chicago, 1957, The Year Book Publishers, Inc., 195 pages. Price $4.00.

This excellent manual is the outgrowth of mimeographed notes for second-year medical students at the University of Pennsylvania Medical School started several years ago. Its purpose is to acquaint the student with the methods of physical diagnosis used in the examination of the infant and child. Perhaps the chief criticism is that it may be too complete and elaborate for the medical student.

Microtechniques of Clinical Chemistry for the Routine Laboratory. Samuel Natelson, Springfield, Ill., 1957, Charles C Thomas, 484 pages. Price $11.00.

This book defines the need for the terminology of microanalysis. It then proceeds to describe the equipment needed and the proper technique required for sampling and handling of samples. The majority of its chapters are directed to the microdetermination of almost any substance that a modern laboratory might be expected to run. Measurements are for the most part made with standard laboratory equipment. This book also contains a good bibliography as well as a list of manufacturers of micro equipment.

A. F. H.

The Year Book of Pediatrics. Edited by Sydney S. Gellis, M.D., Chicago, 1957, The Year Book Publishers, Inc., 469 pages. Price $7.50.

The 1957 year book, as usual, contains excellent abstracts of pediatric articles appearing through May, 1957. Many are followed by editorial comment. Dr. Gellis maintains the high standards set by Dr. Poncher a few years ago.

Fun Comes First for Blind Slow-Learners. Mildred B. Huffman, B.E., M.A., Springfield, Ill., 1957, Charles C Thomas, Publisher, 157 pages. Price $5.00.

Mrs. Huffman is a teacher at the California School for the Blind and has the position of teaching retarded blind children, a task most of us would consider hopeless. In this monograph she tells of the methods she has developed and used in her work and the achievements of the children under the program.

Editor's Column

THE CANNED BABY FOOD WAR

FOR many years, since the canned baby food business was started by Clapp in the early twenties, we have watched the growth of the industry and its ups and downs, as it has been of interest and importance to pediatricians. Much of the advertising, particularly in the early days, has been directed toward gaining their support.

The canned infant food products filled a need, and have played a definite part in improving infant nutrition and in making life easier and happier for hundreds of thousands of mothers. The growth of the industry in recent years has been phenomenal. According to a report in *Barron's* of last February 10, while the increase in the birth rate, 1947 through 1956, rose about 10.5 per cent, the tonnage of canned infant foods shipped during this period increased by nearly 45 per cent. The estimated annual dollar income from sales during this period increased from around $109 million to over $300 million, or nearly 60 per cent.

Clapp, the first company in the field, was started in the kitchen of a home, and its ownership has changed hands several times. It now is a division of Duffy-Mott, engaged chiefly in apple products, and if memory serves correctly, was at one time owned by American Home Products. Clapp started by retailing through the drug stores, but Gerber, who entered the business later in the twenties as a side venture of a canning factory, used grocery stores as an outlet and set the pattern in use today. Gerber today holds the number one position in the industry, with around ninety canned items, and is said to account for roughly one-third of the total sales volume. Next come Heinz and the Beech-Nut Life Savers companies. The annual infant food business of the latter is estimated around $50 million. Other companies are the Clapp, and Libby. Mead Johnson is reported as acquiring the Bib Company. To these must be added the meat packers such as Swift and Armour, who process canned meats for infants. While prohibited from canning vegetables, they supply the meat for the meat-vegetable combinations. Armour is said to supply Gerber, and both companies market the Gerber products containing meat. A similar arrangement between Beech-Nut and Swift is reported as having been switched to Hormel.

Naturally intense competition has developed with so many companies engaged in a struggle for the same market, and percentagewise the profits from sales has fallen, although the earnings are substantial. Some of the companies have centered on the use of

glass containers, and others on less expensive metal. There has been a definite shift toward glass in recent years, which was the original form of the container used by Clapp. There has been a geographical element involved in the distribution and use of the products of the different companies, with the sales of one company leading in one section of the country and another leading in some other section.

While the products of the canned food industry have played a part in what might be described as the "harmony" of life and living, in that they have led to an improvement in the well-being of infants, and hence to happiness and peace in the home, there is considerable "disharmony" among the companies in the industry. While this in no way involves the pediatrician, who will continue to use the useful products brought out by the rival companies, the rows that have developed are of interest to him as he is very much involved in the use of the various products.

Financial papers have recently reported that suits have been brought by the Gerber and by the Heinz companies against Beech-Nut, charging unfair competition in California, with violations of the Sherman, Clayton, and other Acts of Congress. Damage suits aggregating $26 million have been filed. Many charges are involved: price differentials, false advertising, unfair promotions, rebates, etc. One of the claims reported as a basis for one of the suits is that Beech-Nut representatives bought out the entire product of one of the companies in some supermarkets, so that only their own products would be left on the shelves for customers. Naturally there are denials and counterclaims.

It usually takes many months and even years before such suits come to trial. We have no opinion as to the right or wrong of the claims made by the companies involved. The products of the companies, however, have been an important contribution to infant feeding and nutrition and are designed for use as advised and directed by the pediatricians. For this reason the pediatricians have an interest (not financial) in the companies, and the outcome of this internecine warfare will be closely followed by those of us with seats on the sidelines.

Under the circumstances it might be a wise precaution if the booths of the warring companies were widely separated in setting up the commercial exhibits at pediatric meetings, so that as innocent bystanders we will not be hurt if the cans begin to fly.

MEDICAL SCHOOLS AND MEDICAL STUDENTS

AT PRESENT there are 83 *approved* medical schools in the United States, of which 79 have 4-year programs. Two others, Florida and Seaton Hall, will become eligible in 1960 when their first classes are graduated, and a 4-year school at the University of Kentucky is scheduled to open in 1959. In the 1956-1957 school year there were 29,003 medical students enrolled in the 83 schools, and, in addition, 127 attending the two schools mentioned above. Ten years previously, 1946-1947, the number of medical students enrolled was 23,900. Thus an increase of 21 per cent in the number of students has taken place in the ten years.

The rush for higher education which led to so many seeking admission to the medical schools following World War II has eased. For the entering class in 1949 there were 3.5 applicants for each place available. By 1955 this had dropped to 1.9. The situation, however, is beginning to reverse itself, and medical educators believe that by the mid-sixties there will be a return to the 1949 situation. The average applicant continues to apply for admission to several schools. In 1956 there were close to 16,000 applicants who filed nearly 60,000 applications or 3.8 per applicant. This varies little from the figure for a number of past years.

The teaching responsibilities of the medical school faculties are not limited to the teaching of the 29,000 medical students. In 1956-1957 the schools carried teaching responsibilities to 63,000 other students, as interns, residents, fellows, postgraduates, and advanced students, and to dental, pharmacological, and nursing students.

The demand for more doctors will increase in the years to come with a rapidly increasing population and with so many in the old age group. The ratio of 133 doctors to every 100,000 of population in the United States has changed little in recent years. The demand for more doctors for services of a governmental nature, and for industry, is steadily increasing. The Association of American Medical Colleges in 1956 recommended that the increase in the number of physicians needed should be met by increasing the number of medical schools. In 1957 the Association proposed that the universities should be encouraged to develop programs that would offer the first two years of the medical course. A survey has shown that the present 4-year schools have facilities to train between 300 and 400 additional third and fourth year students. This proposal has been concurred in by the Council of Medical Education of the American Medical Association.

One of the common misstatements, not infrequently heard, is that an applicant for admission to a medical school to be accepted must have had a college "A" grade scholastic average. The actual percentage of students admitted to the entering class in 1956 by college grades was as follows: "A," 16.1 per cent; "B," 69.9 per cent; "C," 14 per cent.

Along with everything else the cost of a medical education is steadily rising, bringing a very disturbing financial factor into the determination of who will be the doctors of the future. Tuition fees in 1956-1957 averaged $720 for resident students and $918 for nonresidents, as compared with $684 and $857 for 1955-1956. The difference between resident and nonresident involves the state-supported schools.